UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE, S.A. and ROCHE PALO ALTO, LLC,

Plaintiffs,

-vs-

DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.

Defendants.

CIVIL ACTION NUMBER:
11-3962

TRIAL

Clarkson S. Fisher United States Courthouse
402 East State Street
Trenton, New Jersey 08608
June 4, 2015

B E F O R E: THE HONORABLE MARY L. COOPER
UNITED STATES DISTRICT JUDGE

Certified as True and Correct as required by Title 28, U.S.C., Section 753

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I N D E X

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(In open court. June 4, 2015, 9:30 a.m.)

THE COURT: Good morning, everyone. Okay. Are we ready to go to work today? Would you like to call your next witness?

MR. WONG: Yes. Good morning, Your Honor. My name is Jovial Wong. I represent the Teva defendants. Good to see you again.

As our first witness defendants call Dr. John Freuhauf. He will be discussing more about the efficacy of palonosetron.

(Whereupon, JOHN FRUEHAUF, witness for the defendants, sworn.)

THE DEPUTY CLERK: Please state and spell your full name for the record.

THE WITNESS: John P. Fruehauf, F-R-U-E-H-A-U-F.

VOIR DIRE EXAMINATION BY MR. WONG:

Q. Good morning, Dr. Fruehauf.

A. Good morning.

Q. Dr. Fruehauf, have you been asked to provide expert opinions in this case?

A. Yes, I have.

Q. And, in general, what do your opinions relate to?

A. They relate to the clinical development of palonosetron.

Q. Okay. Let's do a little background first, Dr. Fruehauf.

Where are you currently employed?

A. University of California Irvine.

Q. And what is your current position at the University of California Irvine?
A. I'm a professor of clinical medicine and the director of clinical pharmacology and developmental therapeutics.
Q. And is there a particular cancer center that you work at at UC, Irvine?
A. I work at the Chao Family Comprehensive Cancer Center.
Q. And what is a comprehensive cancer center?
A. It is a cancer center -- there are 43 comprehensive cancer centers in the United States, and this is one of those. They're designated by the National Cancer Institute, and they have to have the complete array of services from basic research to clinical trials development to qualify.
Q. How long have you been at UC, Irvine?
A. Since 1993.
Q. Can you briefly describe your educational history?
A. I went to college at UC Santa Barbara where I got a bachelor's degree in psychology and a bachelor's degree in cellular and organismal biology. And then I proceeded to medical school and did an M.D./Ph.D. program at Rush University in Chicago, and my Ph.D. was in pharmacology.
Q. What is pharmacology?
A. Pharmacology is the study of how drugs work.
Q. Okay. After you got your medical degree in 1985 what did you do?

THE COURT: Just a second. The Ph.D. was in what?
THE WITNESS: Pharmacology.
THE COURT: Okay. And the M.D. was an M.D.?
THE WITNESS: Yes, ma'am.
THE COURT: Then you went on to specialize in your medical training?
THE WITNESS: Yes. Then I did my residency at UC, Irvine, and then I went to do my fellowship. After two years of residency I was in the scientists' training track, so I did four years of medical oncology at the National Cancer Institute in Bethesda and then one more year in biotechnology there.
BY MR. WONG:
Q. Okay. While at the National Cancer Institute, did you participate in clinical trials?
A. Yes, I did. In fact, every patient who we saw at the cancer center had to be on a clinical trial.
Q. After your time at the National Cancer Institute what did you do?
A. Then I went to OncoTech, a biotechnology company.
Q. What was the focus of your work at OncoTech?
A. OncoTech was a company that -- the tumor from the patient would be sent to the laboratory, and we would study the effects of different chemotherapy agents that might be selected for that patient's tumor type. And we looked at the

impact of the drugs on the tumors growing in a test tube, so to speak, and then based on the results we could advise the clinician about, you know, which drug would be less likely or more likely to be effective for that patient.

Q. Okay. Did your work at OncoTech include drug product development?

A. Yes, it did. So, if there were residual tumor cells after performing the primary testing, then we worked with pharmaceutical companies to study their developmental compounds in a preclinical setting against the human tumors, which we felt was more representative than the typical cell lines that most companies would utilize.

Q. Okay. How long were you at OncoTech?

A. Until 2006.

Q. And where did you go after OncoTech?

A. I was working at both UC, Irvine -- as a medical oncologist -- and OncoTech, but I was part-time at the university until 2006, and then I went full-time at that year.

Q. Okay. Now, while at UC, Irvine, what has been the focus of your research?

A. Basically clinical trials, you know, to translate ideas from the laboratory into the clinic, writing clinical trials, carrying them out.

Q. Okay. What does the term or principle "bench-to-bedside" mean?

A. So, bench-to-bedside is really how we were trained at the NCI.

So you would go into the laboratory, do experiments with cell lines and drugs and then come up with maybe a new combination of treatments that you could then go and write a clinical trial and give it to the patients to see if it works better than what was there before.

Q. Okay. And what types of clinical trials do you carry out now?

A. I carry out various clinical trials in different diseases: Melanoma, urological oncology, kidney cancer, bladder cancer.

Q. Do you have experience carrying out all phases of clinical trials?

A. Yes. As director of developmental therapeutics, I'm involved in Phase I, Phase II, and Phase III trials.

THE COURT: What is Phase I, Doctor?

THE WITNESS: Phase I?

THE COURT: To you. You know, I hear what it is from lawyers and that kind of thing, but what does Phase I consist of in your experience?

THE WITNESS: Well, in my experience it is the first time you -- usually there's the first-in-man Phase I. First-in-man. So, the first time you actually take a drug and give it to a human being before it has been given to animals

and put on cells, and this is the first time you're giving it to a person, so it is a safety question.

THE COURT: So, this is healthy volunteers?

THE WITNESS: In the perspective of the situation at hand that would be healthy volunteers.

THE COURT: Okay. Fine. Thank you.

BY MR. WONG:

Q. How many clinical trials are you currently involved with?

A. Seven or eight trials right now.

Q. And does your work at UC, Irvine also include preclinical trial work?

A. Yes. So, I mean, we -- you know, based on my prior laboratory experience at OncoTech I have continued to do the work of sort of correlating what happens in the test tube with what happens in people and trying to figure out are there markers we can study on the patient's tumor, like is there a mutation that would predict the drug will or won't work for that patient.

THE COURT: Do you have test tube laboratories in your --

THE WITNESS: Yes. I train Ph.D. students, so I have a regular, you know, bench laboratory where we grow the cells and tissue culture, and we add the drugs, and flow cytometry and HPLC and stuff like that.

BY MR. WONG:

Q. Getting back to your clinical practice in humans, how busy is your clinical practice?

A. I have three days a week that I see patients, and then there's a month every year that I'm in the inpatient service taking care of all the cancer patients in the hospital.

THE COURT: How do you do both, this kind of heavy research that you're doing, clinical trials and preclinical lab work, and also follow patient charts?

THE WITNESS: So, it is all about protected time. You know, you have to have some protected time to be able to go to the lab and talk to your post doc or graduate students about their experiments and review their data. You go to the clinic and, so, I have a really good nurse, and I have a good post doc, and those people help me tremendously in managing things on a daily level. So I become more of a supervisor. But the patient care takes the most time.

BY MR. WONG:

Q. Over in your entire career, about how many cancer patients do you think you have treated?

A. Oh, you know, more than 1,000.

Q. Now, as part of your clinical oncology practice do you have experience with supportive care of your patients?

A. Yes. At the time I trained at the National Cancer Institute there wasn't really a palliative care specialty yet, which does do supportive care today, and, so, we were trained

to support the patient with pain medications, antinausea medications, antidiarrheal medications just to really support the whole patient.

So, I grew up out of that experience, and, so, to this day I'm trying to manage the quality of life for the patient concomitantly with the intervention for their -- to treat their cancer.

Q. Okay. Can you explain your experience with antiemetics?

A. Unfortunately today we still use chemotherapy for the vast majority of cancer patients. And, so, as a result we need to be giving medications that will suppress nausea and vomiting.

And as research into the mechanisms of what causes this process in people, drugs have been developed that attack the different sort of pathways that stimulate nausea and vomiting.

So, today we sort of use an amalgam of agents that will attack different pathways so you're simultaneously suppressing the impulse to throw up and to feel sick.

So, there would be Marinol, for instance, for cannabinoid receptors; NK-1 -- Emend is an NK-1 receptor inhibitor; the 5-HT receptor inhibitors, such as palonosetron and Compazine. I give Compazine frequently, which is a dopamine receptor suppressor.

So, it is really combining drugs that work on different pieces of the process of nausea.

Q. Okay.

THE COURT: And these receptors are not just in the brain, right?

THE WITNESS: No. There's the gut process, which is where serotonin signaling starts in the body. It is all built on the concept of an evolution you don't want to eat poison. So when your gut senses a poison, your body wants to extrude it, so it sends a signal to the brain stem to throw up, basically.

BY MR. WONG:

Q. And in addition to your research at UC, Irvine do you also teach?

A. Yes. I teach an undergraduate class every fall, so it is coming up, and it is about 250 undergraduate students that are upper division. And I'm teaching --

THE COURT: These are not medical students?

THE WITNESS: No. This is undergraduates, and they are pharmaceutical sciences majors, and they're mostly prepharmacy, but there are subsets that are premed and preindustry. And I teach the fundamentals of drug development, the clinical phases of drug development, concepts of how does the membrane and the receptor work for drugs. Basic concepts that would help them in the future.

BY MR. WONG:

Q. Aside from undergrads, do you teach any other students?

A. Yes. So, I teach, of course, medical students, residents, and fellows. And next month I'll be giving a core lecture to the new fellows that are just starting on melanoma and how we approach melanoma. So, you know, I enjoy teaching.
Q. Okay. Do you teach your students about clinical trials?
A. Yes. So, the undergrad class, that's a big component of it, because so much of what you do as a pharmacist is you're, you know, giving drugs, and you need to know, sort of, how do we come up with these package inserts and how -- what does the drug have to go through to finally be accepted?
Q. Okay. Outside of UC, Irvine are you involved with any professional organizations in your field?
A. Yes. I'm a member of the American Society of Clinical Oncology, the American Association of Cancer Research, which are the two big meetings for sort of the bench and bedside presentations on results, and, you know, some local organizations.
Q. Okay. Have you also published papers in the field of oncology?
A. I have about 80 peer-reviewed publications.
Q. Okay. Are you yourself also a peer-reviewer on relevant journals?
A. Yes. I peer review articles. I got a text message this morning about I'm late on reviewing a manuscript, so I review for Cancer Research, Clinical Cancer Research, you know,

various cancer journals.
Q. Okay. Have you ever served as an expert witness in a patent trial?
A. Yes, I have.
Q. How many?
A. In one trial.
Q. And in that trial, generally speaking, what was the expertise that you were offering?
A. It was about the preclinical and clinical development of pemetrexed.
MR. WONG: Your Honor, defendants tender Dr. Fruehauf as an expert in the clinical sciences and pharmacology with a focus on oncology and supportive care.
MR. O'MALLEY: No objection.
THE COURT: Admitted.
MR. WONG: Thank you.
DIRECT EXAMINATION BY MR. WONG:
Q. Okay. Dr. Fruehauf, let's get right to your opinions.
In forming your opinions in this case have you reviewed the '219 patent?
A. Yes, I have.
Q. And have you reviewed the asserted claims of the '219 patent?
A. Yes, I have.
Q. Let's see the '219 patent. It is DTX-0268. Let's go

right to the claims on Page 11.

And, Dr. Fruehauf, in your opinion what is the subject matter of the '219 patent?

A. I think the subject matter of this patent is related to a formulation that maintains stability for 24 months of the compound, the active pharmaceutical ingredient, palonosetron.

Q. Okay. In your opinion who would a person of ordinary skill in the art be with respect to the '219 patent?

A. A formulator.

Q. Are you a formulator?

A. No. No, sir.

Q. What is your training in?

A. I'm a medical oncologist and a pharmacologist.

Q. Okay. So, how is that relevant to a POSA -- can I use the term "POSA" for a person of ordinary skill in the art?

A. Yes.

Q. How is your training relevant to a POSA for the '219 patent?

A. Well, my expertise would be applied more to the administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting. Cancer chemotherapy-induced nausea and vomiting. And I'm trying to stick with mainly what's in the text there, but I do paraphrase, and I apologize.

THE COURT: Maybe if you slow down just a little bit.

We have plenty of time.

THE WITNESS: Yes, ma'am.

BY MR. WONG:

Q. If we call that "CINV" is that okay?

A. Yes, sir.

Q. Okay. So, with respect to this part of the claim, what type of expertise are you offering for the '219 patent?

A. The clinical development component where how did they come to this conclusion that the drug is effective at reducing the risk of nausea and vomiting, and this is -- really the key is to reduce the likelihood of cancer chemotherapy-induced nausea, and that stems from the clinical trial data.

Q. Okay. Do you have preclinical and clinical expertise?

A. Yes, sir.

Q. Okay. Have you prepared a demonstrative to explain the various types of clinical trials?

A. Yes, I have.

Q. Okay. Let's have Fruehauf 2. Can you walk the Court through this general paradigm of preclinical and clinical trial processes?

A. So, this is an overview.

THE COURT: Just a second. Give me a moment. I'll be right with you. Okay. So, you have s demonstrative here. Go right ahead.

THE WITNESS: So, this is an overview of the

preclinical -- so that's before it gets to people -- and the clinical trial process. And, basically, this is what I discuss with my undergraduate students, but there's a preclinical phase. Somebody conceives of a drug or, you know, let's say a drug that would have an intended purpose to improve people's outcomes.

So, they have to test it in animals to show that it is safe in animals, and they'll have animal models that would be reproducing the human state that they're trying to mitigate.

So, for instance, they could use ferrets and give them high doses of chemotherapy like Cisplatin, and the ferrets would vomit. And they can then give the ferret the drug that they're developing that's supposed to suppress vomiting and show that at a certain dose for that animal, where the drug reaches a certain concentration in the animal's blood, it effectively suppresses the nausea.

So, that's the test of effective, and coming up with the dose in animals that's so critical to, you know, going to the FDA with this information of safety and efficacy to ask if we can give this to people. And the safety part is basically giving higher and higher doses of the drug to animals over an extended period of time and then sacrificing the animals and looking at all their organs through the microscope and checking their biology, their kidneys still function, is their liver fine, and so on and so forth.

And, so, if you can find that at the doses needed to be effective in the animal model that it doesn't cause toxicity in the animal, then you go to the FDA and you file an Investigational New Drug Application. And that's this interface right here.

And when you go to the FDA with this information and you say, This is my plan in Phase I, I'm starting at a much lower dose than was found to be safe in the animal. I want to give a group of healthy volunteers this drug, and I'm going to give increasing amounts of the drug to make sure that as I go up and up and up in the doses that are given to people that I can cover the dose that I can, you know, predict was working in the animals.

So, I'll give a model dose that worked in animals to people in Phase I and find out if that's safe.

THE COURT: So, these folks are not suffering from nausea?

THE WITNESS: No, ma'am.

THE COURT: You're just checking for safety?

THE WITNESS: Yes. And when I was a medical student I would go in and work with the Phase I studies. These are usually younger people who are getting paid to come in for three days, and we give them the medicine, and we check their blood pressure and draw their blood and check their blood levels just to prove that in a normal human being there's no

unexpected adverse event.

And, so, once we have gone up through this range of doses, and we have determined that it is not toxic and, also, that we have confirmed that we can give a dose in humans that are normal without an illness that matches the dose that was effective in animals, then we take these two pieces of information, we go back to the FDA and we say, Okay, we would now like to now prove that the drug is effective for the intended purpose on a group of patients, and that is the Phase II goal.

So, in Phase II of the trials we are determining if the dose we found is safe and is similar to the dose that was effective in animals will now be effective in humans.

And, you know, these study designs tend to be unblinded usually, and we would just give the drug to the people who are let's say cancer patients that are going to get chemotherapy that's highly nausea-provoking or highly emetogenic and see if the drug would prevent that nausea.

And if we have success here, in other words we have defined an effective dose in Phase II, then we go and ask the FDA, Do you agree that we have defined the effective dose, and, if so, can we take this into a larger Phase III trial where we can confirm in a larger group of people and do more safety analysis, and critically here in Phase III, compare the new drug with what's already out there that it would be

equivalent or better than the existing therapies.

Then if these Phase III studies are effective -- it might just be one, two or three, it is not critical how many, but if your Phase III study is effective, then you go and ask for your New Drug Application approval so that you can commercialize the agent.

MR. WONG: Okay.

THE COURT: And you can select a couple of two or three different dosage levels to put into your Phase II or Phase III trials, right?

THE WITNESS: Absolutely. And I think that, you know, certainly in this case that's what was done.

BY MR. WONG:

Q. Okay. Now, Dr. Fruehauf, is this how drugs are currently tested for safety and efficacy?

A. Yes. This is the current process, and it goes back to the sixties when there was realization of the need for a sort of codified process that everyone could follow where, you know, these safety signals would be identified early and then that if you thought it was really working you could really prove that on a statistical basis.

Q. Okay. Now, who is carrying out these types of preclinical and clinical studies?

A. So, the preclinical studies would be done, you know, by scientists, pharmacologists, you know, Ph.D.s, and then --

THE COURT: Ph.D.s in what?

THE WITNESS: Pharmacology, cell biology, physiology. So, the preclinical work is mainly done by that level of person, and then when you go into people, of course, now we're talking about patients or even healthy volunteers, but if you're giving a drug to a person, you have to be a physician.

THE COURT: Yes.

THE WITNESS: So, that's where we start as clinicians in Phase I.

BY MR. WONG:

Q. Okay. By 2002 how would you characterize the practice of conducting these clinical trials?

A. Very routine.

Q. Okay. Now, going back to Phase II just to follow up on a couple of issues --

THE COURT: Do you design clinical trials? I know that you supervise them, right?

THE WITNESS: No, I have two INDs right now for two different clinical trials that I'm carrying out for melanoma. So, I have gone through this with the FDA.

THE COURT: The IND is where you go to get permission for Phase I research?

THE WITNESS: Well, actually, so the IND itself carries through all the way until you're done with Phase III.

So you're making sort of amendments to your Investigational New Drug Application as you go forward.

BY MR. WONG:

Q. Okay. Were you in court on Tuesday to hear opening statements?

A. Yes, sir.

Q. Did you hear the term "minimum effective dose"?

A. Yes, I did.

Q. What is the minimum effective dose?

A. That would be the dose that has the sort of optimal effect for the intended purpose, such as, let's say, suppressing nausea, but is the least amount of drug because the more concentration you have in the blood, the more likely it is that the drug will bind to other places besides the intended target and give you side effects.

So, you want to avoid side effects as much as possible, so you want the minimum amount of drug that would have the intended effect.

Q. Okay. And in the clinical trials what does it mean that a trial is "randomized"?

A. So, randomized trials are trials where, you know, let's say there's different arms on a study. You know, for instance, the comparator study here, we have one arm that would be a standard drug that's already approved. Now we have the new drug.

So, you might just have a two-arm study; one for the comparator, one for the new drug, which how do you know what the patient is going to get? You flip a coin or you use a random number generator. And then that patient would be randomly assigned to one of those two treatment arms. And that could go for four arms or three arms, it doesn't matter, but the simple thing would be you flip a coin. If it is three arms, you have a three-sided dice you throw in a sense, and it is just randomly picking.

So, this is to avoid bias. This is to avoid the physician sort of he wants the drug to work, let's say, or she, and, so, the doctor could subconsciously even put the better patient into a given arm. So, this is to avoid bias.

Q. Okay. What --

THE COURT: And if you have got -- you call it an "arm," which would be one substance being tested; another arm would be another substance being tested --

THE WITNESS: Yes, ma'am.

THE COURT: -- and this is probably blinded, so the doctor doesn't know which the doctor is administering, right?

THE WITNESS: Yes. The double-blinded --

THE COURT: We'll get there. I'm just -- arm, "arm" is your term for a given drug that's going to be administered.

THE WITNESS: Or a drug at a given dose.

THE COURT: Okay. Yes. But in randomizing you want

to distribute your population, so you get about as many people in each arm.

THE WITNESS: Balanced.

THE COURT: Right? Okay.

BY MR. WONG:

Q. Okay. Your Honor, you mentioned "blinded."

Dr. Fruehauf, what does it mean when a trial is "blinded"?

A. So, the blinding would be, again, trying to avoid bias. And you don't want people to know, you know, what the patient is getting until after things are done so, there's not bias.

And, so, let's say you've got two drugs in a comparator study. One drug is given in a bag of 50 milliliters of solution through an I.V. The other drug is given as a quick bolus.

Now, obviously, how could you not let the person know if you just gave one or the other? So everybody gets the same. They'll get a placebo, let's say, in the bag and the active ingredient in the injection so that way nobody knows what that patient really got. And the blinding is there's a place where they put the drugs together with a number on it, and then they'll ship it based on the arm the patient is on, and only the people -- nobody really knows what they're getting.

Q. Okay.

THE COURT: And double-blind?

THE WITNESS: So, the patient doesn't know and the doctor doesn't know and the company doesn't know.

BY MR. WONG:

Q. Okay. Just a little more glossary terms. In clinical trials, what does the term "first patient in date" mean?

A. So, you know, let's say you've got your IND and you're in Phase II and -- or you're in Phase III, and you have a protocol. So, the protocol has to go through a review by a review board, be approved, and once it's approved, the patient can be accrued to the study. They have to sign a consent.

THE COURT: Accrued?

THE WITNESS: Accrual is adding people into the study.

THE COURT: Fine. We just want to make sure that's the word you used.

THE WITNESS: Yes, ma'am. Thank you. I know it's like, to me, too much second nature.

So, "accrual" is a term just to put somebody into a trial, and once they have signed a consent, they can be randomized. And once they're treated, that's the first person on, so to speak.

Now, you can really consider once they sign the consent you intend to treat them, and that's -- they're the first person on.

BY MR. WONG:

Q. And then on the other side, what does the term "last patient out date" mean?

A. So, that would be, you know, in the statistical design of the trial, you've made assumptions about what will happen, what the differences might be, and you have a number of patients that you think are required to be able to show what you want the study to show.

And, so, you have a target of end number of patients to be put on the study, and when you've reached that target, that's your last patient, you've met your accrual goal and that's the last patient on. And when they're last patient out is they got the drug, the effect of the drug was measured, and now they're done.

Q. As of the last patient out date in a clinical trial, what does the data look like?

A. So, in a blinded trial, the last patient out, you have all the data and all the results in your spreadsheet. You just don't know which patient got what drug.

Q. Okay. Is the data unblinded at some point?

A. So, once the last patient's out, there's sort of, you know, the term used in the pharmaceutical -- by companies is "cleaning" the data, so they have people that go and make sure all the data is correct, there aren't mistakes of, you know, this number should have been in this box or that box and so

on.

So, they clean the data. And once it is cleaned, they lock the data.

Now, once you lock the data for the FDA, you can no longer change any of the data. That's it. It's fixed.

So, once the data is locked and can no longer be touched, then you can unblind the data, and now you'll know who got what and you can, you know, determine if the drug was effective or not.

Q. Okay. After the data is unblinded, can the data change at all?

A. No. It's been locked, so you can't change the data in any way.

Q. And in your experience in clinical trials, is the unblinding date important to investigators and sponsors of a clinical trial?

A. Absolutely. I mean, they've made an investment of millions of dollars. They want to help people. They want a compound that will do that. They want to know did this study show that the drug works. The physicians want to know. Everybody who participated wants to know.

Q. And when is the first analysis of the unblinded data typically done?

A. As soon as the unblinding is done then, you know, the clock is ticking. You want to get your results analyzed so

that you can put together your NDA application if it's a Phase III study, or if it's the Phase II result, you want to go right away into Phase III.

THE COURT: So, but it's not just the -- you push a button on a computer and out comes the analysis, not quite?

THE WITNESS: It's pretty close to that. I mean, you have in the -- the clinical research -- the clinical -- there's usually a company that's working for the drug company that handles the statistics, and they have the database. So, the database is set up to actually just be the input into the statistical analysis program.

And I've run these programs. I mean, it's not that complicated. So, it could take a couple of days to do an analysis once the data is unblinded.

BY MR. WONG:

Q. Okay. Is the initial statistical analysis of the efficacy data that is conducted -- that is conducted, the initial analysis, is that analysis reliable?

A. Well, the data never changed, and it's all preordained because when you go to the FDA and you say, I want to run a Phase III trial, for instance, you have to tell them what analysis you will do at the end, how you will do that analysis.

So, you have to follow what you already said you were going to do years earlier. So, that is it. That first

analysis is the result of the study based on the preordained process of analysis.

THE COURT: Then why do you call it the first analysis? Can you go back and troubleshoot it?

THE WITNESS: You can't really change the data. Now, what can happen, you know, I've been involved where, you know, we have the primary result and we have the analysis, but we notice something, let's say. We noticed that, gee, it seemed like people that had high blood pressure did better. So we can do what's called an ad hoc analysis of data, but that doesn't change the data. It's just another way of looking at the same data.

THE COURT: And saying, oh, and we also learned this in addition.

THE WITNESS: Correct. But for regulatory purposes, that wasn't preplanned, and so it isn't assigned the same degree of credibility.

MR. WONG: Okay. Thank you, Doctor.

THE COURT: And the analysis is not likely -- you know how if you do -- if you tell somebody to do a numerical computation of some sort and they do it and they bring it to you and you pick it up and you say this doesn't look right, then you find out that they made some mistake in the middle.

THE WITNESS: So, that you have avoided in the data cleaning step because this is so regulated.

THE COURT: Regimented.

THE WITNESS: It's regimented. I mean, there's not room. I mean, I wouldn't say that mistakes are impossible, but there's a tremendous effort with lots of people who work through weekends and nights when this data is being cleaned to get to the result. There's tremendous stress on those people to get it right because if they don't get it right, they get their hand slapped by the FDA.

And, in fact, the FDA has stated that the way pharmaceutical companies do research is far superior to how, let's say, you know, a cancer center would do research because it's so regimented and refined as a process that's become so routine.

BY MR. WONG:

Q. Okay. Thank you, Dr. Fruehauf. Let's get back to your opinions in this case.

A. Yes, sir.

Q. As of the January 30th, 2002 date, was it known that administering palonosetron to humans reduces the likelihood of CINV?

MR. O'MALLEY: Objection; vague.

Known by whom?

Objection; vague. Objection as to form.

THE COURT: Can you rephrase?

MR. WONG: Sure.

BY MR. WONG:

Q. With respect to a person of ordinary skills in the clinical sciences, would that person know as of January 30th, 2002, that palonosetron administered to a human reduces the likelihood of CINV?

A. Yes.

Q. Okay. Have you reviewed the documents in this case that support your opinions?

A. Yes, I have.

Q. Have you prepared a summary of those documents?

A. Yes, I have.

Q. Let's go to Fruehauf 3.

Dr. Fruehauf, what were the key documents that showed that palonosetron reduced the likelihood of CINV by the critical date?

THE COURT: Counsel, before you allow the doctor to answer your question, are you asking him for documents that would be available to this hypothetical skilled artisan?

MR. WONG: That's right.

THE COURT: So, these are public by legal definition?

MR. WONG: Well, for the on-sale bar, it can be private documents, confidential documents, or public documents.

THE COURT: But available to the hypothetical skilled artisan --

MR. WONG: Available --

THE COURT: -- I would think?

MR. WONG: Well, let me ask the doctor this.

BY MR. WONG:

Q. In your analysis of the question of whether a person would know if the palonosetron would work, what kind of documents did you review?

A. I reviewed the Phase II study results from the Syntex trial that was concluded in 1995.

THE COURT: And is that publicly available in 1995, Doctor?

THE WITNESS: No.

MR. WONG: I can ask.

BY MR. WONG:

Q. For your opinions herein today, did you review both public and private, confidential documents?

A. Yes, I did.

Q. Did you rely on both public and private, confidential documents in forming your opinions?

A. Yes, I did.

THE COURT: All right. You may proceed, but I want the distinction to be observed, if you would, please.

Is that your basis, Mr. O'Malley?

MR. O'MALLEY: Yes. He said, as you noted, quite clearly that this would be what a POSA knew. POSAs don't know

our clinical -- our confidential clinical documents. There's no foundation for this slide.

THE COURT: Okay. So, we'll keep this distinction going, and you can ask your questions, Mr. Wong.

MR. WONG: Thank you.

BY MR. WONG:

Q. So out of the documents that you relied on, what were the key documents that formed your opinion?

A. So, I looked at the Syntex Phase II trial, 2330. That was the first study of palonosetron in people that were sick. And I looked at a meeting minutes that Helsinn had, where when Helsinn licensed from Roche who had acquired Syntex, Helsinn had a meeting with the Syntex folks to learn, well, what did we in-license? What's the science that we have now that we've in-licensed this? So, that meeting was in 1998.

And then after their review of this, they sent a letter to the FDA explaining their intentions for a clinical development program. That was November 1999. And then they began their Phase III studies and put out a press release to the effect that we are now carrying out a clinical trial based on results from the Phase II study. We've moved into Phase III.

And I reviewed the Phase III trials. I reviewed the reports for the trials and also a declaration by Cantoreggi who stated, you know, that they knew that the drug was

effective at a certain time.

MR. WONG: Okay. Let's go right to the first document. Can we have the Syntex Phase II trials, DTX-0227. Let's go to Page 5 of the study.

BY MR. WONG:

Q. Dr. Fruehauf, do you recognize this document, DTX-0227?

A. Yes, sir. So, this is the final report on the 2330 clinical trial, which is the dose ranging, efficacy, safety, and pharmacokinetic study of single-intravenous doses of RS-25259, which is palonosetron, for prevention of nausea and vomiting in chemotherapy-naive cancer patients receiving highly emetogenic chemotherapy.

Q. Dr. Fruehauf, were you in court on Tuesday to hear Dr. Calderari's testimony on this document?

A. Yes, I was.

MR. O'MALLEY: And I'll just object until they lay the foundation that your Honor requested as to whether or not the POSA would have had this, since the overarching opinion is that a POSA would have known X.

THE COURT: Okay. Mr. Wong, can you -- is this available to a POSA?

BY MR. WONG:

Q. Would this document have been available to a POSA? Was this document publicly available as of 1995?

A. I don't believe so.

Q. If you saw this document in 1995, would you understand that, and reviewing the data, would you understand that palonosetron was effective to reduce CINV?

MR. O'MALLEY: Objection. Calls for speculation.

THE COURT: Sustained.

You can ask him what this document tells him now. That's fine.

MR. WONG: That's fine.

So let's go to Page 14. Let's go right to results or the study synopsis, and let's go to objections down low. The objectives below.

BY MR. WONG:

Q. Dr. Fruehauf, what was a primary -- what was a primary objective of this Phase II study? Looking at this document today, what was the primary objective of the Phase II study?

A. It was, basically, to determine whether palonosetron, over a dose range of 1-90 micrograms per kilogram, given to patients who were treated with highly emetogenic chemotherapy would reduce the likelihood of chemotherapy-related nausea.

Q. Okay. In carrying out the primary objective of this study, would it include a determination of whether palonosetron reduces the likelihood of CINV when administered to humans?

A. Yes.

MR. WONG: Let's go to the methodology section.

Right below.
BY MR. WONG:
Q. Dr. Fruehauf, how would you characterize this Phase II Study 2330?
A. This is a very strong Phase II study because it was randomized and double-blinded in multicenter, so in multicenter trials, you have a variety of people participating, which decreases bias.
And then it was this dose-ranging efficacy study, so they wanted to know what dose is working to suppress nausea. So it was a very strong design for a Phase II trial.
THE COURT: You said not all Phase II trials are even blinded at all.
THE WITNESS: Correct.
THE COURT: This was?
THE WITNESS: Yes.
MR. WONG: Okay. Let's go to the next section, the number of subjects section.
BY MR. WONG:
Q. Dr. Fruehauf, how many patients in total were involved in this Phase II Study, 2330?
A. There were 161 patients, more males than females, and then there were 13 patients who were excluded from the efficacy analysis for various reasons, which, you know, we won't go into, but -- and, so, it was 161 patients with 13

excluded.
Q. And how many patients actually got the 0.25 milligram dose of palonosetron?
A. There were -- which is the equivalent of 3-micrograms-per-kilogram dose. Of 3 micrograms per kilogram, .25 was the equivalent to 3 micrograms per kilogram, and there were 24 patients who received that dose.
Q. So, did the study design of this Phase II study allow the determination of whether palonosetron administered at 0.25 milligrams reduces the likelihood of CINV when it was administered to a human?
A. Yes.
MR. WONG: Let's go to summary and conclusion section on Page 15.
BY MR. WONG:
Q. Right here in the first sentence, what was Syntex's conclusion on this Study 2330?
A. They concluded that all four doses, and they're talking about 3, 10, 30 and 90, they didn't -- .3 to 1 was a low dose that wasn't expected to have the full effect, but it did have some effect because no drug would have lead to, you know, zero control of nausea and vomiting.
So, they found that 3, 10, 30 and 90, let's take the percent complete control going across, those were equivalent and effective. All four doses were approximately equally

effective as compared with the combined results from a cohort of the .3 to 1 micrograms per kilogram.

Q. And what do they state in the first sentence?

A. They state that palonosetron was administered as a single bolus intravenous injection of these doses 30 minutes prior to chemotherapy.

Q. So, let's focus in on the --

THE COURT: And that they were looking at suppressing CINV for 24 hours after the chemotherapy.

THE WITNESS: Yes, ma'am. So, the endpoints here were complete control at 24 hours, which means, by definition in the study, that they didn't throw up and they didn't feel nauseated. They didn't need a medicine to help them after they got the first medicine.

And then this is a second endpoint, complete response, where the numbers were a little lower because that would be those patients might have needed some rescue medicine, and then the median time --

THE COURT: What's the difference between complete control at 24 hours and complete response at 24 hours, can you tell us?

THE WITNESS: Yeah, this is really the difference between who needed a rescue medication, and the percentage of people -- like this is a lower number for complete response because they might have felt nauseated. They didn't throw up,

but they might have felt nauseated. They filled out a questionnaire --

THE COURT: Yes.

THE WITNESS: -- about how they felt over the 24-hour period --

THE COURT: Yes.

THE WITNESS: -- and they used that questionnaire to assess the benefit of the drug for its intended effect.

THE COURT: And that last row says, "median time in hours to failure defined as first emetic episode or rescue drug."

THE WITNESS: Yes. So that is, you know, basically, they got the medicine, they got the chemotherapy, and how long did the medicine work for? When did it wear off?

So when it wore off, that means you're starting to feel sick. And that's the delayed emesis. And, so, let's say for the .25 or the 3-micrograms-per-kilogram, that time to failure was 22.7 hours, compared to, let's say, 19 for 10, greater than 24 for 30, and 21.8 for 90. We can see these numbers are all pretty consistent, but these numbers are lower, so there's sort of a --

THE COURT: In other words, the dosage beginning with 3 and going up was pretty consistent. It's just the dosage below 3 that fell off.

THE WITNESS: So, you know, what we understand about

palonosetron is it was very potent. And, you know, you're binding to a receptor, and if you -- if you have enough drug to bind to all the receptors and they're all blocked at a certain dose, giving more drug won't have any more benefit.

THE COURT: Doctor, we're talking about this H --

THE WITNESS: 5-HT.

THE COURT: -- 5-HT_3 receptor. That's not the only receptor that sends signals of nausea to the brain, is it?

THE WITNESS: No. As I was explaining earlier from my practice, I will combine drugs that will work on different receptors because here there's only a 50 percent control.

THE COURT: Even at best --

THE WITNESS: Even at best.

THE COURT: -- with palonosetron.

THE WITNESS: With one drug. So, if you give a second drug and a third drug, now you're going to improve your control rate to some degree; but, of course, as you add more drugs, you're getting into more side effects.

THE COURT: But the other drugs would target other receptors theoretically.

THE WITNESS: Correct.

THE COURT: Thank you.

THE WITNESS: So, here we have a saturation of the receptors, and as you go higher, you don't really see any change after that.

BY MR. WONG:

Q. Let's just focus on the 0.25 milligram data that's under 3-microgram-per-kilogram. What do the data, 46 percent, 39 percent and 22.7 hours, based on those data what can you conclude about whether 0.25 milligrams of palonosetron reduced the likelihood of CINV in patients who got this dose?

A. It's very clear that it effectively reduced the risk. I mean, if there was zero here, from my clinical experience if you don't give any premedication to someone who's getting highly emetogenic chemotherapy, 90 percent of them are going to throw up.

THE COURT: Because that's nature's way --

THE WITNESS: That's nature's way.

THE COURT: -- is that right?

THE WITNESS: They get a poison, they want to throw up. So, you have to have something in there to suppress that natural reaction to the poison that we're putting in their veins.

And, so, this was partially effective, and then this was the maximal effect, I think, in this Phase II trial.

THE COURT: You're referring to the Column 3.

THE WITNESS: Yes.

THE COURT: The column under the Dosage 3.

THE WITNESS: Right. So this is -- these percentages of control are similar as they stated, all four doses were

approximately equally effective. So these are all kind of the same. So this would be the minimal effective dose in this particular set of doses.

THE COURT: Referring to the column under 3.

THE WITNESS: Yes, ma'am.

THE COURT: When you use a pointer, the record, the cold page of the record, doesn't know which column, so I'm just filling that in for you. You don't have to worry about it.

THE WITNESS: Understood. Thank you. I'll try and --

MR. WONG: Thank you, your Honor.

Okay. Let's go back to the timeline, Fruehauf 3.

THE COURT: Okay.

MR. WONG: Unless you have any other questions.

THE COURT: I wonder, could we take a recess now? Would that be all right?

THE COURT: Back in session.

MR. WONG: Thank you, Your Honor.

BY MR. WONG:

Q. I think we left off on Fruehauf 3, the timeline. Dr. Fruehauf, just wrapping up on the Syntex Phase III Study 2330. What is the date of the study report, Study 2330? What is the date of the study report?

A. The date of the study report was July, 1995.

Q. Now, if a person of skill in the clinical sciences were to see the data in the Syntex study, on or about 1995, would he or she come to the same conclusions that we just discussed?

MR. O'MALLEY: Objection, Your Honor. No foundation. We've already received testimony that that POSA could not have seen it.

MR. WONG: Your Honor, my question is just if that person were to see this document.

THE COURT: I'll permit it. Experts can be asked hypotheticals. I agree with you that there's not a fact upon which they could base this hypothetical, but I'll permit the question.

MR. LOMBARDI: Your Honor, at some -- maybe not now, but at some point it might be helpful to address the role of POSA in the ready-for-patenting analysis because it's different than the prior art and there's not a requirement that a person of skill in the art have seen the public data.

THE COURT: Okay. Let's defer that. Don't want to argue it now.

MR. WONG: Thank you.

THE COURT: Go ahead and make your record, Mr. Wong.

MR. WONG: Okay.

BY MR. WONG:

Q. The answer to my question was? Let me read the question again.

If a person of skill in the art in the clinical sciences were to see the Syntex data as of 1995, would he or she come to the same conclusions that we just discussed?

A. Yes, I think it would be clear that the drug at the .25 milligram dose reduced the likelihood of nausea and vomiting.

Q. Okay. Let's move on.

What is the next document you considered in forming your opinions?

A. The July, 1998 Helsinn meeting minutes.

Q. And what is important about this document, this meeting minutes from July, 1998?

A. Well, this is really where Helsinn was taking the reins of the development process. And they needed to assess what they had, and this is really their interpretation of what the drug had done so far.

Q. Okay. Let's go to DTX-0015.

Okay. Let's orient ourselves. Is this the Helsinn meeting minutes that you relied on?

A. Yes, it is.

Q. Okay. And what is the title here of this document?

A. This is Helsinn Palonosetron Team Meetings, palonosetron --

THE COURT: These are all internal people?

THE WITNESS: So, these were -- yes, these were people from Syntex. There were some Syntex people --

THE COURT: Okay.

THE WITNESS: -- and then there were -- no, they weren't all inside people. And then there were Helsinn people, and then there was an outside expert that was invited to the meeting.

THE COURT: They were paid to come by somebody?

THE WITNESS: I don't know. Probably.

THE COURT: Okay.

BY MR. WONG:

Q. Where were these meetings held?

A. In Palo Alto, California.

Q. And when did these meetings take place?

A. In July of 1998.

Q. Let's take a look, let's enlarge it and see who attended these meetings. So when you say outside consultants, what outside consultants attended the meeting?

A. A Dr. David Gandara from UC Davis.

Q. Do you know Dr. Gandara?

A. Yes, I do.

Q. Who is Dr. Gandara?

A. Dr. Gandara is a medical oncologist who has published widely on antiemetic chemotherapy trials, on chemotherapy for lung cancer. He's published more than 100 papers. His papers have been cited by more than -- each paper, might be a thousand people have cited his paper. So he's very well

respected in the oncology community.
Q. Now, based on your review of these meeting minutes, what was the purpose of these meetings?
A. The purpose of the meeting, as I stated, was to understand on the -- from the perspective of Helsinn, what did Syntex do, what were their data, and how could we go forward in the regulatory process.
Q. Okay. Let's go to Page 8. This is DSC, Page 8. What does this -- if you blow it up a little bit more.
What does this portion of the -- in general, what does this portion of the meeting minutes disclose?
A. So, this discloses the doses that I'm pointing out here under the overview, where it states, "The following drug doses and concentrations are proposed for the CINV and PONV trials." So the chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting trials.
And then below that, they have the CINV table, where they list a dose of drug that would be put in the 5 milliliter volume, with the concentration listed next to the dose, and the dose chosen for CINV was .25 -- or doses, .25, .75 and 2.
Q. What were these -- on what data were these doses chosen? Based on what data were these doses chosen?
A. The discussion at the meeting was about the Phase II trial, and based on the Phase II trial results, as we described, you're trying to identify in Phase II the minimally

effective dose, and so they've taken that Phase II trial result and now they're proposing to take these doses forward into Phase III.

Q. Were all three doses actually studied in Helsinn's Phase III trials?

A. No, they reduced it down to .25 and .75, just those two.

Q. And just to be clear, as shown in this table for CINV, what was the concentration of the formulation where the dose was 0.25 milligrams?

A. The concentration was 0.05 milligrams per milliliter.

Q. And was the design of the Phase III clinical trials also discussed at these team meetings?

A. To some degree, yes.

Q. Let's go to Page 10. And let's -- first two paragraphs. This is DTX, Page 10, first two paragraphs. So under CINE study designs, what does Helsinn say about the Phase II studies?

THE COURT: We've already established that CINE is synonymous with CINV.

MR. WONG: Correct, Your Honor.

THE COURT: Do you see it that way, Doctor?

THE WITNESS: Yes, ma'am.

THE COURT: Okay.

THE WITNESS: Emesis or vomiting --

THE COURT: All right.

THE WITNESS: -- are equivalent.

BY MR. WONG:

Q. So let me repeat the question.

What does Helsinn say here about Phase II studies?

A. It says that, you know, that they don't want to use a low dose because that wouldn't be ethical because it wouldn't have as much control, so they're proposing to test the effective doses seen in Phase II, and as we've stated, these were equivalent, according to the conclusion from the Phase II study. So we're going to take these equivalent doses in a sense and compare them to ondansetron at 32 milligrams which at that time was the standard dose for ondansetron to prevent chemotherapy-induced nausea and emesis.

THE COURT: Just saying this, ondansetron, 32 milligrams, compared to a quarter milligram or three-quarter milligram of palonosetron.

THE WITNESS: Yes, ma'am. And this is because the -- we use the term "potency," and so the mechanism of the drug is completely different. It doesn't compete with serotonin. So they have a receptor, serotonin would come and bind to the receptor. You can try and block that. Now you've got to have more of your drug than there are serotonin molecules to keep it from binding and signalling nausea.

But what palonosetron does is it binds a different place, and the receptor goes off the surface of the cell. And

you don't have to compete with serotonin anymore because you've down-regulated the receptor completely. So this was a, you know, second-generation drug.

BY MR. WONG:

Q. Okay.

THE COURT: Palonosetron?

THE WITNESS: Yes, ma'am. Palonosetron was a second-generation 5-HT inhibitor.

BY MR. WONG:

Q. Just for the record, these -- these weighted doses of 3, 10 and 30 micrograms per kilogram, what do they equal when you turn them into fixed doses?

A. .25, .75, and 2 milligrams.

Q. And what was the injection volume that Helsinn selected for these doses?

A. The volume is planned to be 5 milliliters.

Q. If a person of skill in the clinical sciences were to see this information, how would he or she interpret the information?

A. That Helsinn interpreted the Phase II trial results to indicate that the .25 milligram dose was the minimal effective dose, and they were going to take that with a couple of other doses that were higher into the Phase III study.

MR. WONG: Let's go to Page 12. If you could blow up the top section.

BY MR. WONG:

Q. What is the title of this section of the meeting minutes?

A. This is entitled "Gandara Meeting."

Q. And with respect to the section, dose selection, what does it state regarding Dr. Gandara?

A. So, after meeting with Dr. Gandara and his review of the data, it states that the dose selection, and then we'll just quote what it says, "Gandara recommended that, despite the unusual result in 2332," which was an oral trial, not an I.V. trial, that the 3 microgram per kilogram was most likely the correct dose for chemotherapy-induced nausea and vomiting.

Q. Do you agree with Dr. Gandara's recommendation here?

A. Yes, I do.

Q. And why is that?

A. Because I think it's clear from the trial that the .25 milligram dose was the inflexion point, and after that you've saturated the receptors and that that's the minimally effective dose and you want to avoid higher doses because, as you go up on doses, you're more likely to get side effects. So Dr. Gandara came to the same conclusion that I have, and he's recommending that he thinks that the 3 microgram per kilogram dose was most likely the correct dose for CINV.

THE COURT: For intravenous administration?

THE WITNESS: Yes, ma'am, for intravenous administration. Not for oral administration.

BY MR. WONG:

Q. Let's go back to the timeline, Fruehauf 3. Dr. Fruehauf, what is the next document that you considered after the July, 1998 meeting minutes?

A. I considered the 1999 Helsinn letter to the FDA.

Q. Were you in court when Dr. Calderari testified about this document?

A. Yes, sir.

Q. Okay. Let's go to the document DTX-0293. Just to remind the Court, what is this document, DTX-0293?

A. So, as we heard from Dr. Calderari, Helsinn could not directly communicate with the FDA because they did not have a subsidiary in the United States. So they had to hire a consulting firm to communicate on their behalf to the FDA. So the Austin, Texas, August Consulting Company was hired by Helsinn. And this is a letter to the Center for Drug Evaluation and Research at the FDA, where they are providing now on their INDs -- so they have licensed-in this IND which was already filed by Syntex, and they're amending it to go to the next step. Their proposal is now to go to three new Phase III protocols, PALO-99-03, PALO-99-04 and PALO-99-05.

Q. Did they actually attach the protocols to this letter?

A. Yes, sir.

MR. O'MALLEY: I'm sorry. I hate to interrupt. But, again, the foundational question we've been requesting as to

all these documents and the Court has has not been established.

THE COURT: I think that's fine for you to note your objection when each document comes up, but we'll keep going.

MR. WONG: Let me repeat my question.

BY MR. WONG:

Q. Were the Phase III protocols, the proposed protocols, attached with this letter?

A. Yes, sir.

Q. Okay. Let's take a look at the protocols. Let's go to Page 21.

What is disclosed here?

A. So this is the 99-03 protocol which was basically addressing the question of single I.V. doses of palonosetron at the .25 and the .75. Now, they've, you know, just chosen these two, lower doses, versus ondansetron at a 32 milligram dose, in the prevention of moderately emetogenic chemotherapy-induced nausea and vomiting.

Q. Okay. And what is the date of this proposed protocol?

A. November 15th, 1999.

Q. Let's go to Page 34 in this document. And this is into the 99-03 proposed protocol. What is shown here at the bottom of Page 34?

A. So, what is shown here is, you know, they have to have the justification for the FDA on dose selection. They have to

provide the data to the FDA for their protocol, and any investigator -- I mean, when I review protocols and I'm on our investigation, you know, IRB, Investigation Review Board, and I review maybe half of all the protocols that come through. And I want to know, well, should we open the study here, did the drug work? Has it been effective? I mean, could we expect a good result for our patients and our institution?

And so in the protocol, you need to be showing what the drugs did and why you picked, you know, this dose, for instance. And so they're just reiterating what we've already reviewed which was the Phase II data, to support their dose selection for the .25 milligram dose by giving the data from the Phase II study.

Q. And what does Helsinn say about this data on the next page?

THE COURT: Just a second. Doctor, the data in the table is the same as we saw.

THE WITNESS: Identical.

THE COURT: Right. The first column, the labels that they use are a little different.

THE WITNESS: Here, it's percent with CR, so complete response.

THE COURT: Complete response.

THE WITNESS: And then CC was the complete control, and then here was the time to failure where we saw, you know,

the -- that number of hours it took before people actually got sick.

THE COURT: And what does this p-value refer to?

THE WITNESS: So the p-value is the probability that the result seen could have occurred by chance alone, and in a smaller trial like this where there's small numbers of people per arm, you know, you're really looking more for the trend or, as Dr. Calderari said, the signal. And so the probability that 46 percent control occurred by chance is one chance in 10 that that occurred by a random event.

THE COURT: Okay.

THE WITNESS: And then this one says that there is one chance in a hundred that this time to failure occurred, you know, as a -- is a mistake.

THE COURT: So that's just a statistical explanation?

THE WITNESS: It's a statistical explanation, and the way I, you know, look at these data is that since these were pretty much equivalent, you can kind of combine all this and be -- you know, it's very clear that the drug reduced nausea and vomiting, and you could look at this number and say, gee, there was this statistically significant, even with these small numbers, delay in time to failure for the .25 dose.

BY MR. WONG:

Q. Okay. So let's go to the next page, and what does Helsinn say about this Phase II data on the next page? Let's

blow up the first paragraph.
A. So, you know, as part of their protocol proposal to the FDA, again, they have to give the rationale for the dose selection. And so, they're saying that data from this Phase II study clearly demonstrate that the 3 microgram per kilogram dose or the .25 milligram dose of palonosetron is the minimal effective dose in preventing chemotherapy-induced nausea and vomiting.
Q. Okay. And do you agree with this statement to the FDA?
A. Yes, I do.
Q. Okay. Now, are you surprised that Helsinn is making this statement in this proposed protocol for its Phase III trial?
A. No, as I said, they need to have a statement about what the result was from Phase II. So Phase II, as we've said earlier, the goal is to find the minimally effective dose. So they're making the statement here that they did do that, they were successful in their Phase II trial, and that the minimally effective dose is the .25 milligram dose.
THE COURT: So they're building on their Phase II work?
THE WITNESS: Yes, ma'am.
BY MR. WONG:
Q. If a person of skill in the art in the clinical sciences were to see this statement to FDA, would they interpret the statement the same way?

A. They would interpret this statement as to indicate that the Phase II study showed that the .25 milligram dose could reduce the risk of nausea and vomiting.

Q. Let's go back to the timeline, Fruehauf 3.

Dr. Fruehauf, what is the next document that you considered in forming your opinions?

A. The Helsinn press release.

Q. Let's go to DTX-1227. The Court has seen this document, but let's just orient the Court.

Were you in court when Dr. Calderari testified about this document?

A. Yes, sir.

Q. Is this the Helsinn press release that you're referring to?

A. Yes, it is.

Q. What is the date of this press release?

A. September, 2000.

Q. Was this press release public, made public as of September, 2000?

A. Yes, it was.

Q. Let's go to the third paragraph.

In the third paragraph, what does the public press release state about Helsinn's Phase II trials?

A. The public press release states, "The Phase II trials demonstrated the efficacy of palonosetron in the prevention of

emesis with no significant side effects."
Q. Okay. If you read this press release as of September, 2000, what would you understand about this disclosure?
A. I would understand that, you know, they were pleased with their results. They had accomplished what they wanted to in terms of they licensed the drug that had a successful Phase II trial as an underpinning of its further development and that palonosetron did reduce the risk of nausea and vomiting.
Q. Would a person of skill in the art in the clinical sciences understand that Helsinn knew that palonosetron reduced the likelihood of emesis?
A. Yes.
Q. Is it unusual for a company to issue a press release about their clinical trials?
MR. O'MALLEY: Objection, foundation.
THE COURT: I'll permit it.
BY MR. WONG:
Q. Based on your experience.
THE COURT: You read the public literature?
THE WITNESS: Yes, ma'am.
THE COURT: And a lot of other literature?
THE WITNESS: Yes, ma'am. I get --
THE COURT: Technical literature, you read also?
THE WITNESS: Yes, ma'am.
But I'll get e-mails, you know, like this not

infrequently from clearinghouses that follow the press releases and then they send them to us so that we have -- are kept abreast of where drugs are in development because, of course, we're waiting for the next new thing for our patients.

And so -- and as the, you know, chief scientific officer Oncotech for -- for 14 years, we put out press releases, and we wanted to know -- you know, we wanted to let our clients know what we were doing and that we weren't just standing still, that we were making progress as a business. So I think that this is an example of a company that wants people to know that they are moving forward.

BY MR. WONG:

Q. For the record, this press release was issued by who?

A. Helsinn.

Q. Would a person of ordinary skill in the clinical sciences view the statements in this Helsinn press release differently had it been issued by a larger pharmaceutical company?

A. No, sir.

Q. And you actually reviewed the Phase III clinical trial reports?

A. Yes, sir.

Q. Okay. How many were there?

A. Three.

Q. Okay. And what were they called?

A. 99-03, to use shorthand, 99-04 and 99-05.

Q. And, in general, what were the differences between the three Phase III study reports that Helsinn conducted?

THE COURT: That's in the record. We can move on.

MR. WONG: That's fine. Thank you, Your Honor.

BY MR. WONG:

Q. Let's look at the first study report, PALO-99-03, DTX-0288, and let's go to Page 3. Dr. Fruehauf -- you can blow up the entire -- thank you.

Dr. Fruehauf --

A. Yes, sir.

Q. -- do you recognize this document?

A. Yes, I do.

Q. Is this the final study report for 99-03?

A. Yes, it is.

Q. When was the study started?

A. The study was initiated with the first patient in in August 1st, 2000.

Q. And when was the study completed?

A. The last patient out was October 2nd, 2001.

Q. And when was the study report written?

A. This report was written July 19, 2002.

Q. Does the study report describe the batches -- does the study report describe the batches used in the clinical trial PALO-99-03?

A. Yes, it does.

Q. Let's look at Page 7; let's go to the bottom section.

Dr. Fruehauf, what doses of palonosetron were administered in the 99-03 study?

A. You know, as we have stated previously, .25 and .75 milligrams of palonosetron.

Q. And for the .25 milligram dose, what were the batch numbers?

A. The batch number -- the batch number for the .25 milligram dose was 1737321 and HPA003.

Q. Okay. Does the study report provide the final efficacy analysis results?

A. Yes, sir.

Q. Let's go to Page 9 and under the summary section, efficacy results. Let's look at Table 1. What does Table 1 report?

A. Table 1 reports that patients with a complete response rate during the first 24 hours after chemotherapy, which is the same endpoint as we looked at for the Phase II trial, and it shows that the -- for the zero- to 24-hour time period, that in this case, palonosetron at .25 had an 81 percent complete response rate.

Now, just -- this number is about double, you know, almost the prior number we looked at, and that's because this study looked at moderately emetogenic chemotherapy, whereas the Phase II study was done for highly emetogenic

chemotherapy. So we would expect a higher number in this trial than in the Phase II trial.

Q. Does the data in Table 1 show that 0.25 milligrams of palonosetron reduces the likelihood of CINV when given to a human?

A. Yes, it does.

THE COURT: The likelihood --

MR. WONG -- of CINV.

THE COURT: Reduces it, yes.

MR. WONG: Right.

BY MR. WONG:

Q. Okay. And does the study report provide a plan for how the data was analyzed?

A. Yes, it does.

Q. Let's go to Page 56 of DTX-0288, in the bottom portion under 5.8.1. Dr. Fruehauf, how was the data analysis performed?

A. Well, the data analysis was performed according to the preplanned protocol. So before anybody went on this study, it was determined that this is what they would do. And then now the study is done and this is what they did, and they --

Q. How -- go ahead.

A. And they used a SAS software program which is a statistical analysis package. I used that in graduate school. I use a little more modern ones today, but the SAS company was

the most common and widely accepted statistical package for running analysis, statistical analysis for clinical trials.

Q. Does the analysis plan indicate when the data was closed?

A. It states that the database was closed or locked on 19 December, 2001.

Q. Does the statistical plan indicate when the database was unblinded?

A. It was unblinded on January 2nd, 2002.

Q. Did you review any initial analysis of the unblinded data from PALO-99-03?

A. Yes.

Q. And when was the initial analysis performed?

A. January 7th, 2002.

Q. Are you surprised that within a week of the unblinding dates, preliminary analysis of the data was performed?

A. No. As we discussed earlier, people want to know the answer. You know, if it's Christmas day and Christmas morning and you're eight years old and you're looking down under the tree, there's a package for you, you're not going to just sit there. You're going to run over there and open it. This was their first chance to see what were the results of this trial they've worked so hard to carry out.

Q. Analyzing the unblinded data?

A. Analyzing the unblinded data.

Q. Let's go to DTX-0264. Dr. Fruehauf, do you recognize

this document?
A. Yes, I do.
Q. What is this document?
A. This is a document, again, August Consulting, representing Helsinn to -- it's a letter to the FDA, and it's a request for pre-NDA meeting, and that really means that they are putting their regulatory package submission in for licensure for the new drug application, and they're going to come in with their data to support that licensure.
Q. Okay. And what is the date of this letter?
A. The date of this letter is February 7th, 2002.
Q. Did you rely on this document in forming your opinions in this case?
A. Yes, sir.
Q. Was there anything attached to the letter?
A. Yes, there was.
Q. Okay. Let's go to Appendix 1, starting on Page 9. And if we can blow up the entire page on Page 9.

So, what was attached to the letter?

A. So, what we have here is the analysis of the unblinded data from the SAS output. And if we could blow up the bottom of the page here, down here, we can see it says, SAS, analysis tables, printed, 7 January, 2002. So this would be that SAS output, and then it further states that this is confidential property of Helsinn Healthcare S.A.

Q. And what -- based on your experience, what does that indicate to you?
A. That indicates to me that these data were available for Helsinn's review on January 7th, 2002.
Q. In your experience, would you have expected that people at Helsinn would have seen this document on or about January 7th, 2002?
A. In my experience, they would want to see it as soon as possible, yes.
Q. All right. Let's look at the data on Page 9. So let's just take the first row. That starts zero to 24 hours. What does the data look like for the 0.25 milligram dose?
A. The data for the .25 milligram dose in the first column, under treatment group, shows an 81 percent control, complete control -- complete response, not complete control, excuse me -- complete response, 81 percent complete response during the zero- to 24-hour period.
Q. Okay. If you saw this data on January 7th, 2002, what would you know about the efficacy of 0.25 milligrams of palonosetron to reduce the likelihood of CINV?
A. You would know that it did reduce the likelihood of chemotherapy-induced nausea and vomiting.
Q. And what does the 81 percent indicate again?
A. That 81 percent of the patients did not have nausea or vomiting during the first 24 hours -- pardon me?

Q. Go ahead.
A. -- did not have nausea and vomiting in the first 24 hours after receiving that dose of palonosetron, 30 minutes prior to their chemotherapy.
Q. Have you compared this initial analysis of the data here to the analysis of data that was included in the final study report of PALO-99-03?
A. Yes, I have.
Q. Let's go to Fruehauf 4. Dr. Fruehauf, what is shown on the top portion of this document?
A. So the top portion of the slide is the SAS output table from the January 7, 2002, SAS run, you know, analyzing the data, the unblinded data.
Q. And what is shown on the bottom here, Fruehauf 4?
A. And this was the final report which of course, has the identical results.
Q. Is it surprising that the identical results in the final report are identical to the preliminary analysis?
A. They have to be because this was the, you know, pre-stipulated result of the unblinded data which had been locked so it can't change.
THE COURT: When was it locked?
THE WITNESS: It was locked before it was unblinded.
BY MR. WONG:
Q. All right. Let's go to Fruehauf 3 again, the timeline.

And what was the date of the preliminary analysis?
A. January 7th, 2002, which occurred before the critical date.
Q. How does that inform your opinion overall?
A. That, you know, we have a clear understanding from a Phase II study that .25 was the minimal effective dose that was carried forward into Phase III, and in the Phase III trial, that .25 milligram dose was very effective at reducing the likelihood of chemotherapy-induced nausea and vomiting in a prospective randomized trial.
Q. Have you reviewed the other Phase III --
THE COURT: Why do you call it "prospective"? You used the word.
THE WITNESS: Yes, ma'am. Prospective is you plan it in advance, and you do what you plan to do, and you can't change what you plan to do.
BY MR. WONG:
Q. Have you reviewed the other Phase III reports in forming your opinions?
A. Yes, I have.
Q. Those would be 99-04 and 99-05?
A. Yes, sir.
Q. I don't want to go through all of them, but for the record, let's just look at DTX-0289 very quickly. Let's go to Page 2. Dr. Fruehauf, is this the study report for

PALO-99-04?
A. Yes, sir.
Q. What was the start date of the study?
A. May 3rd, 2000.
Q. What was the finish date of the study?
A. December 27th, 2001.
Q. When was the study report written?
A. July 19, 2002.
Q. Okay. Let's go to DTX-0290, Page 2. Dr. Fruehauf, do you recognize this document?
A. Yes, I do.
Q. What is this document?
A. This is the PALO-99-05 clinical trial.
Q. When was the 99-05 clinical trial started?
A. First patient in was July 6, 2000.
Q. When was the last-patient-out date?
A. Last patient out was December 31, 2001.
Q. What was the date of the report?
A. The date of the report was August 2nd, 2002.
Q. Okay. Let's go back to the timeline, Fruehauf 3.
Dr. Fruehauf, have you reviewed any documents that -- from Helsinn to the Patent Office that were helpful in forming your opinions?
A. Yes, I did.
Q. Okay. Let's see DTX-0287, Page 0413. Dr. Fruehauf, is

this the document from Helsinn to the Patent Office that you were referring to?
A. Yes, it is.
Q. Let's start at the top. This declaration was submitted for what patent application number?
A. Patent Application Serial Number 11/129,839.
Q. And what was the title of the patent application?
A. The title was "Palonosetron for the treatment of chemotherapy-induced emesis."
Q. Was this application for one of the asserted patents in this case?
A. No.
Q. So why is it relevant to your opinions in this case?
A. Because this patent application states the date that the declarants say they knew that palonosetron was effective at reducing the risk of nausea and vomiting and that they knew that the .25 milligram dose could do that.
Q. Okay. Let's go to Paragraph 4. And who are the people that -- who are the declarants of this declaration?
A. Riccardo Braglia, Sergio Cantoreggi, and Enrico Braglia.
Q. Let's go to Paragraph 9. Do these paragraphs describe the role of each of the declarants?
A. Yes, it states here that Enrico Braglia and Riccardo Braglia worked with Dr. Macciocchi as he developed the clinical protocol of PALO-99-03, and they participated with

Dr. Macciocchi in the design --

THE COURT: In the decision.

THE WITNESS: -- in the decision -- thank you, ma'am -- in the decision to study palonosetron for the treatment of acute and delayed-onset CINV and worked with him to fund and implement PALO-99-03.

BY MR. WONG:

Q. Okay. Let's see Paragraph 10 below. What does Paragraph 10 state, Dr. Fruehauf?

A. It states that Sergio Cantoreggi also worked extensively with PALO-99-03, was familiar with the work reported in PALO-99-03.

Q. Did the declarants sign this declaration?

A. Yes, they did.

Q. Let's go to the last page, 416. On what date did each of the three declarants sign this declaration?

A. August 23rd, 2010.

Q. Let's go back to the front, Paragraphs 2 and 3. Dr. Fruehauf, please read what is stated here in these paragraphs.

A. Paragraph 2 states, "We submit this declaration to establish that Alberto Macciocchi, Enrico Braglia, and Riccardo Braglia had conceived the invention defined by claim 1 of this application, and reduced it to practice, before November 16, 2001, the date that Dr. Piraccini published

abstract Number 5169 in Blood, Volume 98, Number 11, Part 2."

Q. Paragraph 3 as well?

A. Paragraph 3 states that "In particular, we submit this declaration to establish that Alberto Macciocchi, Enrico Braglia and Riccardo Braglia had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV, and had conducted clinical trials in humans to test this idea, at least as early as October 2nd, 2001."

Q. Okay. Let's go to Paragraph 6 and 7. I apologize for jumping around. What do the declarants attach to this declaration?

A. They attach the clinical study report for PALO-99-03, and they state that, "As can be seen from Page 1 of Exhibit A, Helsinn initiated PALO-99-03 on August 1, 2000, and completed the study on October 2, 2001."

Q. Was Exhibit A the same PALO-99-03 report that we just reviewed?

A. Yes, sir.

Q. Let's go down to Paragraph 11. Let's look at the claim that was pending, and Paragraph 12, as well.

Dr. Fruehauf, what was the claim that was pending at the time of this declaration?

A. This claim states that "A method of treating chemotherapy or radiotherapy-induced acute and delayed emesis in an adult human for five days after an emesis-inducing chemotherapy or

radiotherapy event, comprising administering to said human a single dose of a treatment-effective amount of about 0.25 milligrams of palonosetron in the form of palonosetron hydrochloride prior to said emesis-inducing event, without administering any further palonosetron during said five-day period."

Q. And what do the declarants state in Paragraph 12?

A. And in Paragraph 12, they state that "Exhibit A proves that we had conceived each of the features of this method, and tested the method in humans, before October 2nd, 2001."

Q. What -- how are these paragraphs significant to you forming your opinions in this case?

A. Because it indicates that they're saying that they knew the result, they knew that .25 milligrams was effective to reduce the risk of chemotherapy-induced nausea and vomiting, by October 2nd, 2001.

Q. Let's go to Paragraph 17 and 18. What is described here in Paragraph 17 and 18 of the declaration?

A. This is further supporting their contention, "Thus, we had conceived the idea to use .25 milligram palonosetron for the treatment of acute and delayed-onset CINV, as described in claim 1, at least as early as August 1, 2001," which is the date that PALO-99-03 began.

And, "Mostly importantly, we had successfully tested the method in human patients, and we had done so before

October 2nd, 2001 (the date the study was completed)."

Q. Dr. Fruehauf, in your experience, what does it mean when someone says, "We have successfully tested the method in human patients, and we had done so before October 2nd, 2001 (the date the study was completed)"?

A. In my experience, that would mean that they had some understanding of the result from the study and that it was successful.

Q. Okay. Now, as of --

THE COURT: Just a second. They did get the results of the study but not on October 2nd, right?

THE WITNESS: So they would have --

THE COURT: So what date are you relating to -- so what date are you relating to your answer here?

THE WITNESS: So this is --

THE COURT: Your answer was that in your experience, this sentence would mean that these inventors had some understanding of the result from the study and that it was successful. But your answer didn't give a date.

THE WITNESS: Before October 2nd, 2001.

BY MR. WONG:

Q. Okay. I can follow up with that. So as of October 2nd, 2001, the last patient out date, the data was still blinded. Isn't that right?

A. Yes, sir.

Q. Okay. How could investigators come to the conclusion -- come to any conclusion on the study results when the data is still blinded?

A. So the data is constantly being reviewed, but it's always blinded. And in the protocol, it's stated that there were -- there was an ethics committee that was reviewing the data and constantly analyzing what was happening, so you can know the blinded data, you can know the percentage of all the patients who had control of nausea and vomiting, but you wouldn't know what treatment they were getting.

Q. Okay. Have you prepared some slides to explain this to the Court?

A. Yes, I have.

Q. Okay. Let's go to --

THE COURT: The ethics committee includes Helsinn representatives?

THE WITNESS: Usually they're independent, and Helsinn had hired a German company to be the clinical research coordinator, and I think they picked an ethics committee. And it was stated in the protocol that there was this ethics committee, and they were receiving updates continuously. In the United States, we call it a Data Safety Monitoring Board. And we require, you know, I am first since I'm the chairman of our Data Safety Monitoring Board at UC Irvine. So we're always looking at any bad things that are happening to make a

decision, should we stop that study. I mean, if people are getting really sick and there's not that much benefit, we should stop it.

BY MR. WONG:

Q. Okay.

THE COURT: But -- wait a minute.

Your -- that ethics board, ethics committee, are they working in secret, or are they allowed to tell the proponent of the study how it's going, if no adverse decisions have to be made?

THE WITNESS: So, in my experience in the United States, the pharma company will get a letter from the Data Safety Monitoring Board. The Data Safety Monitoring Board works in secret. It's confidential. They can actually see unblinded data, because they can monitor if the drug is hurting people.

THE COURT: Right.

THE WITNESS: And -- but what we see in our protocols is updates, where the DSMB sends a letter saying, we reviewed the safety, we agree the study can proceed. So they're not revealing anything other than there wasn't futility, because there is sometimes a futility that's reached where you're never going to prove the drug works.

That was not in this protocol. There was not a futility boundary described. But that is the concept that, if

the drug is hurting people and it's never going to be shown to be effective, we should just turn it off. So that's one of the things that Data Safety Monitoring Boards review.

THE COURT: Well, you said two things. You said if it's hurting people, we definitely need to shut down this study, right?

THE WITNESS: Yes.

THE COURT: Then you said futility, it is not working, this thing, we can see from these early results of the Phase III that nothing's happening to help these patients.

THE WITNESS: That would be the ethical --

THE COURT: That would be futility?

THE WITNESS: Yes. That's the ethical principle that if it turned out that, you know, it wasn't working and people were throwing up 90 percent of the time --

THE COURT: No point in putting more of this into them?

THE WITNESS: Yes, ma'am.

THE COURT: Right?

THE WITNESS: Yes, ma'am.

THE COURT: Or putting more of it into more people?

THE WITNESS: Correct.

THE COURT: So even futility is reported back to the proponent of this study --

THE WITNESS: Well, they don't --

THE COURT: -- sometimes?

THE WITNESS: Yeah. If it was -- but, you know, usually what you're seeing is, because it's all so routine, everything has pretty much been worked out carefully, you just get a letter back saying, we reviewed the study and everything looks good and continue.

MR. WONG: Let me ask a --

THE COURT: Steady as you go, in other words?

THE WITNESS: Yes, ma'am.

BY MR. WONG:

Q. Let me ask this question: As of October 2nd, 2001, the last patient out date, was blinded data available?

A. Yes.

Q. And could any analysis be performed on that blinded data as of October 2nd, 2001?

A. In my experience, yes.

Q. Could that analysis give any indication as to whether or not the drug was working?

A. Broadly, yes.

Q. Okay. Can you explain to the judge how that can be? Have you prepared some slides?

A. Yes, sir.

Q. Let's go to Fruehauf 5. Okay. What is here in Fruehauf 5?

A. So these are the unblinded data, where we've already

locked the database and we know who got what.
Q. And what can you -- what would the blinded data look like?
A. So you wouldn't know that 81, 73. You'd only know if you added all these up and averaged it, that would be the overall population control rate. And you could compare that, for instance, to a historical rate for, let's say, ondansetron.
Q. Okay. And let's go to the next slide. And when you compare the collected data for all three arms to the historical control rate, what are the outcomes that could -- that could proceed?
A. There is three possible outcomes. So here would be a historical comparator like ondansetron that has an expected control rate, and then the blinded data which would include the comparator so it would include the two doses of palonosetron in the comparator. But it would be averaged, and if that average is low, that means the two drugs, in addition, were pulling down the benefit rate because they weren't working so the average is actually less. So the new drug was less effective than the comparator drug.
Q. What would the second outcome be?
A. The second would be where, in the next slide, we can see that the blue bar is the same height as the red bar, and it's equally effective. So when we average everything out, the comparator drug and the new drug, let's say, were equivalent

in average to the historical comparator drug.

Q. And what is the third outcome that could happen?

A. And the third one would be where the new drugs are actually a little better than the comparator, and in the next slide, what we'll see is that the blue bar is higher because we're averaging the higher control rate from the new drugs with the comparator, and that gives us an advantage over just the comparator by itself.

Q. All right. As of October 2nd, 2001, the last patient out date, if you did this type of analysis on the blinded data from PALO-99-03, did you prepare a slide to show what that would look like?

A. Yes, sir.

Q. Let's go to the next slide.

Can you explain to the Court what the results would be, what is shown?

A. So, in the protocol, they had actually explained on Page 64 that they had analyzed 7,000 patients who had been treated with antiemetic therapy and come up with a equation, a calculation, they could predict what a given patient, given a certain kind of chemotherapy, low, moderate or highly emetogenic, what ondansetron would do in terms of control rate in that setting. And they used a 70 percent historical efficacy control rate for ondansetron. And they needed to do that to sort of get a sense of how many people do we need to

know that the new drug is going to be as good or better than ondansetron.

And if you average together these numbers which would -- what would be happening in a blinded setting, the blinded data is 74.4 percent compared to 70 percent, so, in my experience, you could reach a conclusion that the palonosetron .25 and .75 were reducing the risk of nausea and vomiting and maybe even a little more than the historical control.

THE COURT: Because they were pushing the ondansetron-only ratio up?

THE WITNESS: Correct.

THE COURT: They were exceeding the ondansetron-only ratio?

THE WITNESS: Yes, ma'am.

MR. WONG: Thank you.

BY MR. WONG:

Q. Now, how does that inform your opinions on the statements made in the Cantoreggi declaration?

A. This supports Cantoreggi's statement.

Q. Thank you.

Let's talk a little bit about the --

THE COURT: Just curiosity. The last patient out is what, October 2001, in the 03 study?

THE WITNESS: Yes, October 2nd, 2001.

THE COURT: Right. So all that blind data is there. It hasn't gone through the cleanup, the quality control?

THE WITNESS: That's correct.

THE COURT: And it certainly hasn't been locked --

THE WITNESS: Yes, ma'am.

THE COURT: -- and then unblinded.

If I'm Helsinn and I wanted to take a peek as of October 3rd, 2001, just to the 99-03 results, can I do that?

THE WITNESS: This is the only thing you can do.

THE COURT: But I can do that much?

THE WITNESS: Yes.

THE COURT: What you've described here.

THE WITNESS: Because it's blinded so you're not compromising the data. The last patient's out. You're not going to change anything.

THE COURT: But you're allowed to see it?

THE WITNESS: Yes.

THE COURT: These gross figures?

THE WITNESS: Yes.

THE COURT: Gross blinded, not cleaned-up figures?

THE WITNESS: In my experience, that's true.

THE COURT: Okay.

MR. WONG: Thank you, Your Honor.

BY MR. WONG:

Q. Let's shift subjects.

THE COURT: I thought possibly, for example, the consulting firm who does the -- for example, you're doing the Phase III clinical trial, Doctor, in your hospital, and you're doing it for a pharma company. Well, you know, what are they allowed to see of what you've got and when?

THE WITNESS: So, the CRO has the data.

THE COURT: CRO is the contract research organization.

THE WITNESS: Yes, ma'am. That's what they'd hired that, the German company, I can't remember their name, to collect the data, implement the study, collect the data. So they had the data. And they could ask for an analysis of blinded data because that's not precluded by the FDA.

THE COURT: Just a minute. You use the word "they." Are we talking about the German CRO company or Helsinn, the customer?

THE WITNESS: Helsinn could ask the German company to take a -- you know, do an analysis of the overall data. It's not compromised, it's not unblinded, and the study is done.

THE COURT: Okay.

BY MR. WONG:

Q. And just for the record, could -- as of October 2nd, 2001, could a person of ordinary skill in the clinical sciences also conduct that same analysis on the blinded data?

A. Yes.

THE COURT: If they could get ahold of the data?

THE WITNESS: Yes, ma'am.

BY MR. WONG:

Q. Let's talk about the formulations that were actually used in Phase II and Phase III trials. Have you performed a comparison of the formulations?

A. Yes.

Q. Let's go to Fruehauf 10. Let's walk through this. What is listed on the left side of the slide?

A. This is the Phase II formulation for the Phase II trial, and this is the Phase III formulation for the Phase III trial.

Q. Okay. And what is the active ingredient in each of the formulations?

A. The active pharmaceutical ingredient is identical, palonosetron .25 milligrams.

Q. And based on your review of the documents, was 0.25 milligrams of palonosetron administered in the formulations for both the Phase II study and the Phase III study?

A. Yes.

Q. What -- let's stick with the Phase II formulation. What are the other components of the Phase II formulations?

A. These are inactive excipients that are just there to support, as we heard from testimony on Tuesday, just to maintain the tonicity, a buffer, water, they're inactive. They have no effect on the intended use.

Palonosetron is the active ingredient. Once injected into a person, only palonosetron is going to mediate an effect to suppress nausea and vomiting. And these other things are just safe and they just get diluted in the blood.

Q. To be clear, do the inactive excipients, sodium chloride -- inactive excipients, sodium chloride, dibasic sodium phosphate, monobasic sodium phosphate --

THE COURT: Counsel, please. Slow down.

MR. WONG: -- water for injection. Thank you, Your Honor.

BY MR. WONG:

Q. -- water for injection, and NaOH solution, do they affect the efficacy of the 0.25 milligram dose of palonosetron?

MR. O'MALLEY: Objection, Your Honor. He said he has no expertise in formulation.

THE COURT: Does it go beyond his report?

MR. WONG: This is right in his report, and if I can lay a foundation.

THE COURT: Okay. Let's see.

BY MR. WONG:

Q. Dr. Fruehauf, are you a pharmacologist?

A. Yes, my Ph.D. is in pharmacology.

Q. Does a pharmacologist -- would a pharmacologist study the effects of the drug formulation when it's administered into the body?

A. Yes. And, as a clinician, I want to know when I give the drug to someone that the things that are in that vial aren't going to do anything to interfere with the drug I'm giving to the patient. So, as a pharmacologist, I understand why they're there and what they're doing. As a clinician, I know they're not interfering with the intended effect of the drug.

Q. And what happens when the Phase II formulation is actually injected into the patient and into the blood?

A. It's the active ingredient by itself that's mediating the reduction in risk of nausea and vomiting.

THE COURT: Why do you use the word "mediating"?

THE WITNESS: It's a pharmacology term.

THE COURT: For --

THE WITNESS: It's just -- I'm sorry. You know, it carries out the effect or it carries out the activity or it carries the -- it is -- it's the business end. Without that, that's where the rubber meets the road. The other stuff is not on the road. Only palonosetron is carrying the car down the road.

BY MR. WONG:

Q. And would that be the same for the Phase III formulation?

A. Yes, sir.

Q. Do the inactive excipients listed in the Phase III formulation impact the efficacy of the 0.25 milligram dose of palonosetron when it is administered to the patient?

A. No, they do not.
Q. If a person of ordinary skill in the clinical sciences understood that the Phase II formulation with 0.25 milligrams was effective for CINV, would that same person -- what would they understand about the Phase III formulation with that same 0.25 milligram amount?
A. They would expect it to behave in an identical fashion.
Q. Let's go to Fruehauf 11. Let's go back to the '219 patent.
THE COURT: May I just ask a quick question about this? I don't want to know much about pH. But pH buffering is something that the formulator always has to keep in mind and has -- somehow this is -- this multidisciplinary formulation process has to arrive at an appropriate pH --
THE WITNESS: Yes, ma'am.
THE COURT: -- for the formula that's involved.
THE WITNESS: Yes, ma'am.
THE COURT: Right? And then it's supposed to stay at that pH while it's in the bottle?
THE WITNESS: Yes, ma'am.
THE COURT: But once it's injected into the body, the body's pH --
THE WITNESS: Yes.
THE COURT: -- affects that, and we don't think about it anymore, for purposes of the problems we're talking about

here.

THE WITNESS: Yes, ma'am.

THE COURT: But the pH in the bottle is important to the formulation?

THE WITNESS: It's more important to the injection process, because when it goes into the vein, it's now going to immediately interact with the cells of the vein.

THE COURT: And the blood inside the vein.

THE WITNESS: And the blood inside the vein. But the vein cells, the endothelial cells that make up the vein, they'll react with the excipients, and if the overall pH is acidic or basic, it would irritate. It wouldn't be balanced with the cells and the blood.

So you're trying to give a neutral -- the pH in the body is 7.4. So you're trying to design a solution that would be 7.4, so when you inject it into the body, it won't irritate the vein because that would be bad. And, you know, we -- and then what happens if it leaked out when it was being injected? Then it's in the tissue. And that can cause an extravasation is the term for -- extravasation is when things leak out, and that's a problem.

So you're trying to really have a balanced pH, balanced pH means around 7.4, so that when it goes into the body, it won't irritate.

THE COURT: Well, 5 is nowhere near 7.4, is it?

THE WITNESS: Well, if we go back, I guess we could look at the formulation. So these --

THE COURT: Phase III is at 5.

THE WITNESS: Right.

THE COURT: Looks like Phase II --

THE WITNESS: This was 7.4. And then they're adding a sodium hydroxide which is basic and a hydrochloride to reach a pH of 5.

THE COURT: Excuse me just a minute, Doctor. Is the Phase II just saline?

THE WITNESS: No. It included a buffer, so the disodium -- dibasic sodium phosphate and monobasic sodium phosphate are buffers, in water, and then there was a --

THE COURT: So buffers to address pH?

THE WITNESS: Yes. And then the sodium hydroxide, hydrochloride are based in acid to give you a final pH of 7.4. Here --

THE COURT: So it was palonosetron, buffered for the pH to match the body's pH, and some saline water.

THE WITNESS: Yes.

THE COURT: Is that what it was in --

THE WITNESS: Yes, ma'am.

THE COURT: -- Phase II?

THE WITNESS: Yes, ma'am.

THE COURT: So then we go to Phase III, and there are

some stabilizers in there, I'm told.

THE WITNESS: Yes. The --

THE COURT: Okay. We won't get to that right now.

THE WITNESS: Right.

THE COURT: But my only question is, we're getting buffering down to 5.0 --

THE WITNESS: They're bringing the pH --

THE COURT: -- give or take a little bit.

THE WITNESS: Yeah. They're bringing it to 5, which is somewhat basic, but when it reaches the blood, because that isn't like acid, it's not like hydrochloric acid, and it's buffered, it will immediately go to the body pH.

THE COURT: So 5.0 is okay for an intravenous --

THE WITNESS: Yes, it can be.

THE COURT: -- formulation of this? All right.

THE WITNESS: It can be, depending on all the other things that are there.

THE COURT: All right. Thank you.

MR. WONG: Thank you, Your Honor.

BY MR. WONG:

Q. Let's go to Fruehauf 11, and let's go back to the claims.

THE COURT: It was apropos of when you put this formula -- Phase III formulated I.V. vial product into the body, does it have any effect that's different in terms of therapeutic effect from what was injected into the body in

Phase II? And my question was, well, does the buffering change the therapeutic effect at all, I guess?

THE WITNESS: And the purpose for this testimony is to say that, no, it has no impact on the active ingredient. But it's very important for other purposes.

THE COURT: Okay.

MR. WONG: Thank you, Your Honor.

BY MR. WONG:

Q. So let's go back to Claim 1 of the '219 patent and this clinical part of the claim that you opined on.

Dr. Fruehauf, considering all of the evidence we reviewed today, what is your opinion as to whether it was known prior to the critical date of January 30th, 2002, whether 0.25 milligrams was -- of palonosetron was -- could reduce the likelihood of CINV?

A. I think it would be clear to a person of skill in the clinical arts, based on the Syntex Phase II study, based on unblinded data analysis of PALO-99-03 where that output was January 7th and Cantoreggi's declaration that would potentially rely on blinded data, that it was clear that the .25 milligram dose reduced the likelihood of chemotherapy-induced nausea and vomiting.

Q. Thank you. We're almost done. Let's go back --

THE COURT: Before we get to the next whatever, line of questioning, I'd like to see counsel at the side for a

moment on the record.

(The following occurred at sidebar.)

THE COURT: I don't have any earthshaking pronouncement at all, but the doctor's most recent answer was, it would be clear to a person skilled in the clinical arts that this dosage of the drug would be effective before the critical date.

Now, he started out his testimony saying, well, a POSA for this drug would be a formulator, not a clinical guy. And now the question is being asked as if the POSA is a clinical guy. And so I'm wondering whether -- I'm not saying that either the pending question or answer was improper. I'm just wondering whether at some point, if I'm being asked to define the POSA for purposes of this overall patent dispute, that the POSA for formulating the excipients that go into the drug might be a different POSA from a POSA evaluating the efficacy, potential efficacy of the active pharmaceutical ingredient in the formulation. And I leave that for you to think about.

MR. LOMBARDI: Just as a preview, Your Honor, we won't discuss it here, but this is something that has been played out through the case and through the definition of POSA, and the way the parties have dealt with the issue, and we can describe that for you now or just let things develop, but you're hitting on a point that is accurate and there is explanation for how this works.

THE COURT: I'm taking a dim view of what you're telling me because in the trial briefs, I think one side or the other said, well, they say POSA is this, and we don't think that that's right, but it won't change the result in this case, so let's move on.

Well, sometimes, the definition of POSA does change the result in the case. And I just don't want to be blind-sided way down the road and have some of this testimony -- some of this testimony elicited by one or both sides, useless to me.

MR. WONG: If I can just add, I don't think there's any disagreement between the parties that the POSA does consult with others skilled in art, the POSA formulator, with others skilled in the art, including those -- including those in the clinical sciences.

THE COURT: A POSA does consult with others of skill in the art -

MR. WONG: -- including those in clinical sciences. I don't think the parties dispute that.

MR. O'MALLEY: There is a dramatic disagreement among the parties regarding the POSA.

THE COURT: Okay, wait. We can't air this now. But before we let go of this witness or maybe even before we do cross, we are going to have to air it. So let's get through the direct, and then we'll have this discussion as best we can. And we won't have our experts in the room.

MR. WONG: Okay.

THE COURT: And then I'll see where we go from here.

MR. WONG: Thank you. Five more minutes, at most.

THE COURT: No, no hurry. I'm glad that we at least are focused now.

MR. WONG: Thank you, Your Honor.

(Sidebar concluded.)

BY MR. WONG:

Q. Thank you.

Let's go back to the '219 patent, Page 1. Now, Dr. Fruehauf, do you have an understanding that plaintiffs' experts disagree with your opinion as to when it was known that palonosetron would reduce the likelihood of CINV?

A. Yes, I do.

Q. And what is your understanding of what plaintiffs' experts say?

A. Dr. Saab, who is a plaintiffs' expert, has said that he believes that you need two prospective randomized blinded trials.

THE COURT: Can you raise your voice just a little bit? Yeah, good.

THE WITNESS: Dr. Saab has stated that you would need two prospective randomized trials such as the Phase III trial here, two of those, to know that the dose reduced the likelihood of nausea and vomiting.

THE COURT: The .25 dose?

THE WITNESS: The .25 dose reduced the risk or likelihood of nausea and vomiting from chemotherapy.

BY MR. WONG:

Q. And what is your opinion as to the standard Dr. Saab is applying to this inquiry?

A. I disagree because I think that one -- the FDA criteria and the Patent Office criteria are two different things. And I think a person of skill in the clinical sciences looks at these data and says, gosh, even just the Phase II study tells me that the .25 dose reduces the risk of nausea and vomiting, and then it's confirmed in the Phase III study that's prospective blind -- double-blinded and randomized. And, I mean, on the strength of those two studies alone, I think that it's clear that the .25 dose was effective at reducing the likelihood of cancer chemotherapy-induced nausea and vomiting.

Q. Thank you.

Now, when was the data from all three clinical reports, all three clinical trials, when was that data completed and fully analyzed?

A. Sometime around August of 2002.

Q. And when was the '219 patent filed?

A. I believe it was January 30, 2003.

Q. So at the time Helsinn filed the patent, did Helsinn have the multiple Phase III clinical trial data that Dr. Saab is

requiring?
A. Yes, they would have had the knowledge of all three Phase III studies, 99-03, 99-04, and 99-05.
THE COURT: As of January 30, 2003, when they file their patent application, is that what you understand, the question?
THE WITNESS: Before that time, in the summer before that -- in the summer of 2002, they knew that from those three trials. Then they filed January 30, 2003.
BY MR. WONG:
Q. Have you reviewed the patent specification for the '219 patent?
A. Yes, I have.
Q. Does the patent specification include any of the completed and fully analyzed clinical trial data from PALO-03, PALO-04 or PALO-05?
A. No, it does not.
Q. Does the patent specification include any Phase I or Phase II clinical trial data?
A. No, it does not.
Q. Does the patent specification include any preclinical data?
A. No, it does not.
Q. Thank you, Dr. Fruehauf. No more questions.
THE COURT: So, at this point, you may step down.

We're not finished with your testimony, but we're going to take a recess now, and I'll have a discussion with the lawyers before you're called back to the stand.

THE WITNESS: Okay. Yes, ma'am.

THE COURT: Okay. Thank you. Watch your step, please.

(Witness left the stand.)

THE COURT: Can I see you back at the side, counsel, on the record.

(The following occurred at sidebar.)

THE COURT: It's 10 of 12, and it's time for a recess. It's time for us to get some food in us, even though it's not like 12:30 or 1 yet. Off the record.

(Discussion held off the record.)

THE COURT: We are going to take a recess now. But when we come back after the recess, I think we need to have some oral argument directed to the issues, whatever they are, concerning the definition of the POSA. As I suggested, that there might be a problem that we need to address, at least preliminarily now, before we continue with the testimony of this first expert. Okay?

MR. WONG: Okay.

THE COURT: So I would like to see you back at -- could we make it 1:00? Take a little extra long lunch? Will that work?

RESPONSE: Yeah.

THE COURT: Okay. This won't be final argument, but I just need to know where we're going with this. Thank you.

(Sidebar concluded.)

(Luncheon recess taken.)

THE COURT: Fine. Let's have whatever discussion necessary before we proceed with the testimony, and if it is appropriate, I think we should exclude our witnesses.

MR. O'MALLEY: We have done so, your Honor.

THE COURT: Okay.

MR. LOMBARDI: Both sides, your Honor.

Your Honor, I'll just start. I understood your question was on the definition of the person of ordinary skill in the art, and I don't think that there's really much of a dispute among the parties.

I'll give you kind of the general statement, and then I'll come back and show you specifics, but to give you the general idea, incorporated into both parties' definition of the person of ordinary skill in the art here is the idea that it is a person who is part of a team that -- that works for the formulation of a pharmaceutical compound.

And incorporated into both parties' definition is the idea that this person would collaborate with others of different expertises. And, so, the way both parties have approached this is that a person of ordinary skill in the art

is, in our case, we say a formulator who would have access to people in other areas, for instance, clinicians -- excuse me; I apologize, your Honor -- clinicians like Dr. Fruehauf to get information and to inform them in their evaluation of what has gone on.

And, so, that is what you see in the briefs.

DJ, if you could...

This is from our trial brief. Under level of ordinary skill in the art, Page 20. And we note that the patents-in-suit relate to the field of intravenous formulations of 5-HT_3 receptor antagonists, which your Honor has heard a lot about. "A POSA in that field is a formulator with a Ph.D. in pharmaceutical sciences, pharmaceutical chemistry, or a similar field involving pharmaceutical formulations."

And then this is the collaboration language: "The POSA would collaborate with persons of ordinary skill in the clinical sciences, for example, Ph.D. pharmacologists or practicing medical doctors with respect to issues regarding clinical safety and dose." So, there's the concept of the clinician, and that's the role that Dr. Fruehauf, obviously, is playing here.

Now, plaintiffs, it is a slightly different definition, but in this respect I believe is essentially identical. I'll show you this is from plaintiffs' trial brief in the section

under obviousness, but this is where they talk about the definition of POSA.

THE COURT: Page what?

MR. LOMBARDI: It is Page 11. And, obviously, your Honor, the definition of POSA is the same for the entire case. It is the same for a patent. You have one POSA is the appropriate definition for POSA for that patent, and whatever issue comes up, the definition of a POSA stays the same.

If you had two dramatically different patents involving different expertise, you could have different POSAs, but for our case, there's just one POSA. And here's what they say the definition should be: "A person actively involved in the development of pharmaceutical products which involves a number of disciplines and requires collaborative teamwork amongst persons with relevant" expertise --

THE COURT: Experience.

MR. LOMBARDI: I'm sorry. -- "experience in designing and developing pharmaceutical drug product formulations that meet all regulatory requirements. As such, a POSA could have a degree in chemistry, pharmaceutical chemistry, pharmacy, medicine, clinical pharmacology, or another pharmaceutical science-related field and experience in designing, developing, evaluating, and/or testing pharmaceutical formulations." And then they talk about our definition.

Defendants' definition is similar, but it's limited to a formulator that collaborates with such medical professionals. Because the asserted claims are directed to, inter alia, treating emesis, however, a composite POSA definition that includes clinical expertise is appropriate to resolve the parties' obviousness dispute.

So, both parties talk about this idea that it's a team in which -- and as you see, we have different definitions about who the precise individual would be, but that individual would have access to others that were part of the team and would rely on others' expertise in their areas of expertise.

So, that's what -- that's what the definition of POSA is for purposes of this case, your Honor.

THE COURT: Would you excuse me? I'll be right back.

MR. LOMBARDI: Yes.

THE COURT: Right back.

(Brief recess.)

THE COURT: Okay. I'm looking at the one opinion, the one substantive opinion that we have filed in this case, which, as you know, had to do with the preamble language and whether it was limiting or not, and I didn't have to get into what a POSA was in that opinion.

But in the related case, you call it 502 -- 505(b)(2) case, Docket Number 12-2867 at Pages -- internal Pages 21 to 23 we picked up a POSA definition that defendants' expert Dr.

Kibbe had supplied, and we had understood there was no dispute about it at that time.

So, with that, I'll hear from you, Mr. O'Malley.

MR. O'MALLEY: Sure.

Going to the claim construction decision you just cited to, our position was that the POSA dispute had no effect on your claim construction decision, and that's as far as we went on that and, truly, it didn't.

In this case, it's teed up, and while it may read similarly in some fashion, there's a meaningful difference between the two definitions.

As Mr. Lombardi indicated, our person of ordinary skill is a person actively involved in the development of a pharmaceutical product, which involves a number of disciplines, including clinicians. Their definition is a pharmaceutical formulator.

Now, that person works with persons in other disciplines, but I'm not aware of any decision that supported the invalidity of a patent based on how a work colleague would have interpreted the prior art to a POSA. And that's essentially the proofs you're going to be getting here. That's the proofs you got this morning.

Dr. Fruehauf doesn't claim to be a formulator, and he didn't interpret anything from the perspective of their POSA.

Now, what is this all about? It goes back to framing

the obviousness question. If you believe -- and you have already ruled, so it's curious that our opponent seems to still be in denial -- but if you acknowledge that this invention is about the treatment of emesis, which you've ruled is a meaningful claim limitation, then framing the obviousness question goes back to what would a POSA, including this clinician looking for a better treatment for emesis, where would he have started?

And if -- they have a problem with that because of all the facts we've alluded to in our opening, the NK-1s coming on the scene, et cetera, et cetera, et cetera. So, to try and push that aside they say, well, it is a formulator. And all he is going to be concerned about is making a more stable formulation of palonosetron. Everything else about what you pick as the active ingredient and so on, all that's out of his bailiwick. So, it's an attempt to sweep that more meaningful issue regarding the preamble language to the side.

Now, where that leaves them, though, I believe, is between a rock and a hard place. All the testimony you heard this morning and testimony you're going to hear about what one of ordinary skill would have done to pick a dose with respect to the dose limitation in our claims, either you're going to hear irrelevant testimony of what the POSA's work colleague would have done -- this clinician, not the POSA -- or you'll hear testimony from a formulator who never picks doses.

Either way, legally irrelevant.

So, I would submit it's a rather fundamental and important disagreement between the parties with respect to the POSA standard.

MR. LOMBARDI: And I don't know if you want to hear more about the legal consequences of this, but I do think it's very interesting to hear Mr. O'Malley articulate this. I don't think it's been articulated before, but I look forward to briefing this, because I think this shows why Mr. O'Malley can't have it both ways.

He wants, for purposes of claim construction, to make this an FDA-approved product. You have to have an FDA-approved product as part of it, but he wants it, also, to involve just a formulator because that's who he put on the witness stand was a formulator, was -- you heard from -- we just talked to him for two days -- Calderari, I'm sorry, was a formulator. But, anyhow, I can talk about what I believe are just rank inconsistencies in what --

THE COURT: He came along here as a fact witness.

MR. LOMBARDI: He did. But, your Honor, I would say what happened at Helsinn is indicative of exactly what both parties have said is going on with a person of skill in the art.

He was a chemist, a formulator, who dealt with others. He dealt with clinicians. He dealt with other scientists in

informing his opinions on what he was going to do.

Now, I think you say that by analogy. I think that is similar to the situation in the real world with formulation and clinical approvals. You have teams. They deal together. They interact together.

So, somebody like Dr. Fruehauf could be talking to somebody like Dr. Calderari -- I can't believe I'm having trouble with that name already, Judge. I apologize.

THE COURT: It's going to get worse.

MR. LOMBARDI: I think it probably will be.

But you would have people like Dr. Fruehauf talking to chemical formulators. That's the way it works. I'm not aware of any case that says that you can't have that kind of POSA definition. In fact, we've seen it in other cases, and, your Honor, you probably referenced it in the DRL, the related case. I think your definition of POSA that you adopted there did make reference to the collaboration.

THE COURT: It was yours.

MR. LOMBARDI: Yes. Well, not mine. We weren't there, but DRL's. But it is included in the definition.

But the bottom line here is that a POSA includes this collaborative effort. And, so, the collaborative effort means that a formulator would be -- talk to a clinician about what the meaning of the trials meant. The clinician would be talking to the formulator about stability issues --

THE COURT: You're repeating, I know.

MR. LOMBARDI: Okay. So, I'm sorry. I'll stop. And I will save for later what I think are very problematic inconsistencies in plaintiffs' position, but that I think is probably better dealt with on briefing.

THE COURT: I'm not going to rule on it right now anyway.

MR. LOMBARDI: Okay. But that, I think, that's our position.

THE COURT: I see.

MR. O'MALLEY: I just want to correct something Mr. Lombardi said. He said, well, we put a formulator up; but letting aside your accurate observation, he was a fact witness, the difference is our definition is broader. It includes anyone involved in the development of pharmaceutical products, a multidisciplinary team. That's the only -- that's the only POSA who can develop a new drug product.

You need a formulator. You need a clinician. Dr. Fruehauf is a person of ordinary skill under our definition. He is not under theirs. So, there's no contradiction. Our definition is simply broader.

And, again, it gets back to the point of the preamble and is it meaningful? And if it's meaningful, how in the world is a formulator alone going to develop this new treatment for emesis?

MR. LOMBARDI: And, your Honor --

THE COURT: No.

MR. LOMBARDI: No?

THE COURT: No.

MR. LOMBARDI: Okay.

THE COURT: Okay. From there.

MR. LOMBARDI: Okay. From there.

We are not trying to pigeonhole this into just a formulator. As counsel knows, we are calling -- he referenced specifically the obviousness inquiry. You'll hear from a formulator, and you'll also hear from a clinician on our side on obviousness.

And on the preamble, we are not ignoring the preamble at all. We're trying to keep -- we understand exactly what your Honor's ruling was, and we're conforming to that ruling and we're making our proofs conform to that ruling.

What we're objecting to, as I think your Honor has probably picked up, is the idea that that ruling indicates that FDA approval is somehow incorporated into the claim terms of the patent, which we say there's absolutely no support for. And that's our position.

THE COURT: Okay. This has been a useful discussion. I don't have any trouble hearing, so far, the expert testimony that I've heard couched in terms of whoever is speaking within the range of their expertise. Later we'll figure out who this

hypothetical construct person of ordinary skill regarding these patents is, and I don't think that we are losing the benefit of going forward with testimony now with each of these experts.

If they render an opinion as they do from the standpoint of a POSA, you can incorporate your definition of POSA and have it in front of them, and I will understand that they are speaking from the definition of POSA that the party bringing the witness is proposing. I think that's the best I can do right now.

MR. O'MALLEY: Thank you.

THE COURT: Okay. So, you can put it on an index card. Put it up here with your expert, and you can state for the record at that time that you're incorporating by reference your proposed definition.

Will that at least get us moving forward?

MR. LOMBARDI: No problem from our point of view.

MR. O'MALLEY: Yes, your Honor.

THE COURT: Okay. Good.

MR. LOMBARDI: Should we bring the witness back into the room, your Honor?

THE COURT: Sure.

MR. LOMBARDI: Okay.

MR. O'MALLEY: I have a book of exhibits for the witness.

THE COURT: Okay. Fine.

MR. O'MALLEY: And the exhibits we use will be in the books, but they'll also appear on the screen, whichever is easier.

THE WITNESS: Okay. Thank you.

I can do that. Thank you so much.

CROSS-EXAMINATION BY MR. O'MALLEY:

Q. Dr. Fruehauf, you've been retained by Teva in this case to offer opinions as to how a person of ordinary skill in the art in clinical sciences would have interpreted various information; is that correct?

A. Yes, sir.

Q. Now, Dr. Fruehauf, you finished your fellowship in oncology in 1992; is that correct?

A. Yes, sir.

Q. And since 1992, you've been at UC, Irvine where you've been involved in laboratory and clinical research; is that correct?

A. Approximately.

Q. In the two decades since then, you've only been involved in one clinical trial, I believe you told me, involving antiemetics; is that correct?

A. Yes.

Q. And that clinical trial, I believe you testified, was so long ago you do not remember the details; is that correct?

A. True.
Q. But, in any event, that antiemetic trial did not result in an FDA-approved drug; correct?
A. No, it did not.
Q. And in the two decades that you've been at UC, Irvine, you've only worked on two or three trials that resulted in FDA-approved methods of treatment, correct?
A. Yes.
Q. And those trials did not involve antiemetics, correct?
A. No.
THE COURT: Correct? Yes?
BY MR. O'MALLEY:
Q. No, it's not correct?
A. No, they did not involve antiemetics.
Q. Okay. Thank you.
In fact, the emphasis of your research efforts has not been on research or clinical trials that will get a drug approved, correct?
A. No, that's not correct.
Q. So, you say that the emphasis isn't so much to work on a drug that will get approved --
THE COURT: You're talking emphasis? Emphasis.
BY MR. O'MALLEY:
Q. Emphasis.
So, it's your testimony today that the emphasis of your

research hasn't been so much to work on a drug that will be approved because that's what big companies do. That's not your testimony today?

A. I don't think I gave that testimony today. I'm happy to try and --

Q. Is that accurate? Yes or no?

A. No.

Q. Okay. Let me show you your deposition transcript.

A. Thank you.

MR. O'MALLEY: And, Roy, if you can give me Page 18, Line 24 to 20, Line 6.

BY MR. O'MALLEY:

Q. Okay. So, the question was: "It could be participation in Phase II trials that eventually lead to an approved method of treatment by the FDA. So, with that understanding, are there any others beyond the Votrient®" -- and you understand the context was regarding clinical trials that lead to an FDA-approved method of treatment; you understand the context of that question?

A. Yes, sir.

Q. And then I'll read the full answer for the sake of the record: "Well, I guess the GOG trial on Avastin®, that was the Phase II study of Avastin®. I participated in the translational endpoints for evaluating markers that would predict response to Avastin® in ovarian cancer and then

subsequently, it has been approved now for ovarian cancer. I'm, you know, working on the biomarkers for cervical cancer. It was just approved for cervical cancer, and I'm participating in an R21 grant study on markers linked to treatment response in cervical cancer.

"But the emphasis for investigators in the university setting at a comprehensive cancer center where I am, the emphasis is not to do the pharmaceutical company trials as much as it is to develop your own trials and do your own investigations because the NCI values that. And when you receive the large grant from the NCI -- there's 30, 31 comprehensive cancer centers in the United States -- and, so, to maintain our standing and our grant, the emphasis for our faculty who do investigational clinical trials is to do hypothesis-driven investigational trials rather than the large pharmaceutical trials or to do cooperative group trials.

So, the emphasis isn't so much to work on a drug that will get approved because that's what big companies do."

Did I read that correctly?

THE COURT: Read the last sentence. You misread it.

BY MR. O'MALLEY:

Q. Oh, I'm sorry.

"So, the emphasis isn't so much to work on a drug that will get approved because that's what big drug companies do."

Did I read that correctly?

A. You read that correctly.

THE COURT: Sir, Doctor, what does NCI stand for there?

THE WITNESS: National Cancer Institute.

THE COURT: And that's where the grants come from? These grants you're talking about here.

THE WITNESS: These grants come from the National Cancer Institute, and so for promotion in the cancer center program, we're asked to do, to come up with our own ideas for clinical trials; but we still have to do all of the other Phase III trials that we're involved in. So the emphasis academically is what I was talking about.

THE COURT: Okay. Let me ask the questions.

THE WITNESS: Oh, I'm sorry.

THE COURT: I was just looking for what the abbreviation was.

THE WITNESS: Yes, ma'am.

BY MR. O'MALLEY:

Q. So the emphasis of your research efforts has not been on selection of an efficacious dose for a drug to obtain FDA approval, correct?

A. No, that's not correct.

Q. Well, in fact, you've never been personally involved in the selection of a specific dosage of a drug in a treatment that was eventually approved by the FDA, correct?

A. And you asked me that during my deposition, and I was explaining that as clinicians, we are involved --
Q. Sir, can you answer that yes or no? It is a simple yes-or-no question.
A. Okay. I wouldn't be the only one involved in choosing the dose, that's correct.
Q. No, the question is: In fact, you've never been personally involved in the selection of a specific dosage of a drug in a treatment that was eventually approved by the FDA, correct?
A. I'll say yes.
Q. Yes, you've never been personally involved?
I'm just trying to see what your "yes" is. Is that -- did I interpret that correctly?
A. Well, it depends on the definition of "personally involved", but --
Q. Is that what you meant by your "yes"? That's simply the question.
A. Yes, that's what I meant by my yes.
Q. Okay. Thank you.
Now, have you ever done a formal pharmacology research fellowship?
A. My Ph.D. is in pharmacology. There's no fellowship associated with that.
Q. You've never done a formal pharmacology research

fellowship; correct?

THE COURT: Is there such a thing? Are you assuming there is such a thing?

MR. O'MALLEY: I know there to be such a thing, your Honor.

THE WITNESS: I did receive a fellowship grant during my Ph.D. in pharmacology at Rush.

BY MR. O'MALLEY:

Q. Was that what you would consider a formal pharmacology research fellowship?

A. Research fellowship, yes.

Q. Are you associated with the American Society of Clinical Pharmacology and Therapeutics?

A. Not at this time.

Q. Are you associated with the American College of Clinical Pharmacology?

A. No.

Q. Are you board certified in clinical pharmacology?

A. No.

Q. Now, I believe you testified that you're not a pharmaceutical formulator, correct?

A. Correct.

Q. And you understand Teva's definition of a person of ordinary skill, correct?

A. I'm not sure at this time.

Q. Do you understand that it's a pharmaceutical formulator?
A. I believe that's true.
Q. And that's not you, correct?
A. Correct.
Q. However, because the '219 patent involves a method of treating CINV with a specific dosage of palonosetron --
THE COURT: It's actually a compound, not a method patent, counsel, right?
MR. O'MALLEY: Okay.
THE COURT: A composition patent?
BY MR. O'MALLEY:
Q. Okay. However, because the '219 patent has a preamble involving treatment of CINV with a specific dosage of palonosetron, then evaluating that limitation of the patent claims would bring in the experience of a clinician, right?
A. Yes, sir.
Q. Now, you gave an opinion as to written description. Do you understand what I mean by "written description"?
THE COURT: In your expert report, not here.
THE WITNESS: Yes.
BY MR. O'MALLEY:
Q. Well, do you understand that the testimony at the end of your testimony today related to the issue of written description?
A. I understand that.

Q. Okay. In fact, you presented opinions that our patent claims are invalid for lack of written description in your expert report, correct?
A. Yes, sir.
Q. Now, you signed an expert report in this case on August 15, 2014; is that correct?
A. I believe that's correct.
Q. And that expert report accurately reflects the opinions you gave in court earlier today, correct?
A. I believe so.
Q. And do you recall you told me at your deposition that the opinions set forth in your expert report were developed from June through August of 2014? Do you recall that?
A. I believe so.
Q. Now, if you could take a look at DTX-1168 previously marked at your deposition as Deposition Exhibit 4.

MR. O'MALLEY: We're not going to go -- we probably don't need to go into the substance of this, your Honor, but it's in the rack if you need it. It is just a couple questions. Mostly regarding dates and overall content.

BY MR. O'MALLEY:
Q. Do you understand what this document is?

THE COURT: He can read the title. I don't think you can ask him if he understands what it is.

BY MR. O'MALLEY:

Q. Well, let me read the title into the record. It's "Teva Pharmaceutical U.S.A., Inc. and Teva Pharmaceutical Industries, Limited, Invalidity Contentions Pursuant to L.Pat.R.3.6(c)."

Do you see that?

A. Yes.

MR. WONG: Objection. Counsel asked the witness the same question at his deposition, and there's no foundation.

THE COURT: I'll listen.

BY MR. O'MALLEY:

Q. And do you see that this document is dated, and we can go to -- should be .0128 dated March 17, 2014?

A. Uh-huh.

Q. So, this document was completed prior to the time you developed your opinions in this case, correct?

A. I believe so. I'm not really sure about all the dates.

Q. Okay. Well, you told me that your opinions were from June to August, correct? Developed from June to August?

A. It's an approximate -- it's an approximate estimation. I don't know the exact dates.

Q. But that's what you told me at your sworn deposition.

A. Yes.

Q. And you see this is dated a couple months before that, correct?

A. Evidently, yes.

Q. Okay. So, if the dates you told me were accurate at your deposition, then this document was completed prior to the time you developed your opinions in this case, correct?
A. Evidently.
Q. And do you recall we looked at DTX-1168.0093 under heading C?
A. During my deposition?
Q. During your deposition. We'll get there in a moment.
And if you recall, this summarized Teva's opinions regarding lack of written description. Do you recall generally us --
A. Yes.
Q. -- discussing that?
A. Yes.
Q. And at your deposition, you agreed that Teva's invalidity contentions with respect to lack of written description were roughly the same opinion that you provided in your summary opinions in your August 15, 2014 report.
Do you recall that?
A. Yes.
Q. Now, you were not involved in reviewing or preparing any drafts of Teva's invalidity contentions, correct?
A. Not that I know of.
Q. Okay. Now, I'd like to discuss your opinion that you provided at the end of your testimony this morning regarding

the conclusion that the '219 claims are invalid for lacking adequate written description, okay?

A. Uh-huh.

THE COURT: Mr. O'Malley, I do not hear that in Dr. Fruehauf's testimony here, and expert reports are not evidentiary. They're not admitted as exhibits.

MR. O'MALLEY: Your Honor, about five, six questions back, he admitted that that was the gravamen of those opinions that he offered at the end of the day.

THE COURT: He said he was asked questions about those, about that topic.

You can elicit an opinion from him if you want, but I'm sorry, maybe I misheard.

MR. WONG: That's correct, your Honor. I never asked the witness his overall opinion on the written description defense.

MR. O'MALLEY: Okay. We will assume that opinion is not in evidence.

THE COURT: Is that right, Mr. Wong? Not from Dr. Fruehauf.

MR. WONG: To be clear, I asked him about facts related to his review of the patent specification. I did not elicit his overall opinion on the written description defense.

THE COURT: That's right. You didn't.

BY MR. O'MALLEY:

Q. Okay. Now, let's take a look at the '219 patent, and let's look at Claim 1 and look at lines -- let's look at the preamble, and let's start with 4 in the preamble "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting."

Do you see that?

A. Yes, sir.

Q. Now, first of all, in the U.S. in order to treat a human with a pharmaceutical formulation to reduce the likelihood of CINV, that pharmaceutical single-use unit-dose formulation has to be approved by the FDA, correct?

A. You know, there are natural products that are used for reducing nausea in patients, like ginger; but if you're talking about a drug that's for the purpose that's on a package insert, then, yes, it requires FDA approval.

Q. Now --

THE COURT: And you couldn't get a formulation of ginger and inject it.

THE WITNESS: People do things like that.

THE COURT: Okay. Never mind.

BY MR. O'MALLEY:

Q. Now, in your opening expert report -- well, let me strike that.

Today when you were asked about the subject matter of the '219 patent, you said it relates to a formulation and it

relates to stability.

Do you recall that testimony?

A. Yes.

Q. And you didn't state that it relates in any manner to the likely -- to the intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting.

Do you recall you didn't discuss that as part of the subject matter of this patent? Do you recall?

A. No, I did. I said that I believe the patent is based on a formulation for stability, but there is a component within the claim, which was determined to be a limitation, where my being a person in the skill of the clinical sciences impinges on that component of the first section, which is when you start to give things to humans -- now we're not talking about a formulation. Now we're talking about a clinical use and a claim about reducing nausea and vomiting in people, so -- that's related to chemotherapy.

Q. Now, I just want to make sure I understand. Is your testimony now that the preamble is part of the subject matter of the '219 patent?

A. I am not an attorney to make decisions about that.

Q. So, you have no --

A. I'm not a patent attorney.

Q. You have no opinion on that now.

A. I was just -- no. I was asked to give an opinion as a person of skill in the art of the clinical sciences, which is different than a POSA, who's a formulator, to address that element of the claim which was determined to be a limitation, that it's used for treating people with chemotherapy-induced nausea and vomiting. So, they have asked me to come and talk about that part of the claim.

Q. Now, I'm talking about the question you were asked this morning to the effect of what is the subject matter of the '219 patent.

Do you recall that question?

A. Yes.

Q. And do you recall your answer was limited to the formulation and to stability?

A. I believe --

Q. Do you recall that?

A. That's my opinion.

Q. That's your opinion.

So, this preamble then, therefore, logically is not part of the subject matter of the patent.

MR. WONG: Objection.

THE COURT: Sustained. He can't be drawn into that dispute. We've resolved it as a legal matter.

BY MR. O'MALLEY:

Q. Now, in your opening expert report, you state -- you

stated that nothing in the '219 disclosure relates to reducing CINV specifically.

Do you recall that?

A. This morning?

Q. In your expert report.

A. In my expert report?

Q. Yeah.

A. I was referring to the fact that there's no clinical data to support the claim in the body of the patent.

Q. Beyond clinical data, you know or you realize that there's a number of excerpts of the disclosure that discuss treatment of CINV specifically without data; do you realize that?

A. Yes.

Q. Okay. Now, in this afternoon you offered opinions that discussed the fact that there was no data in the patent specification.

Do you recall that?

A. I believe that Mr. Wong asked me if I had seen any of the Phase III clinical trial data anywhere in the patent, and I answered no.

Q. Okay. Now, you're aware that this hypothetical person of ordinary skill in the art has all the relevant publicly available prior art before him or her, correct?

A. I'm not sure what that means.

Q. You're not -- you don't have any opinion on that one way or the other?
A. Maybe if you ask the question a different way.
Q. Well --
THE COURT: It depends for what purpose, I would say.
BY MR. O'MALLEY:
Q. Are you aware that the hypothetical person of ordinary skill in the art for the purpose of interpreting the patent and the prior art has all the relevant --
THE COURT: And the prior art?
BY MR. O'MALLEY:
Q. -- and the prior art has all the relevantly publicly available prior art before him or her?
A. This is a question of the public availability?
Q. That was part of the question, yes. Are you aware of that?
MR. WONG: Objection, Your Honor, to the extent it goes to a legal issue or a legal conclusion.
THE COURT: He can explore a little bit.
MR. O'MALLEY: Do you understand that?
THE COURT: Well, is your question directed to how would a person of ordinary skill in the art, looking at a patent in which they are a person of ordinary skill in the art, read that patent? How would that person understand that patent?

MR. O'MALLEY: Yeah. It is really more general than that with respect to almost any doctrine in patent law; but the point is when Dr. Fruehauf and I discussed this at his deposition, he did have a clear understanding of this doctrine.

THE COURT: Are we talking about claim interpretation, or are we talking about obviousness, or are we talking about on-sale bar?

MR. O'MALLEY: I believe that with respect to all of those doctrines as a matter of patent law, the POSA is presumed to have the prior art in front of him and her and uses that body of knowledge whether it's to interpret what a claim limitation means, whether to judge whether a claim is obviousness, et cetera.

THE COURT: Well, sir, at least -- and this is beside the point of Dr. Fruehauf's knowledge, so give us a second.

THE WITNESS: Yes, ma'am.

THE COURT: At least we know that the POSA looks for certain questions at a patent. He looks at the patent as of the date it was applied for.

MR. O'MALLEY: Very true.

THE COURT: You know, and then for this on-sale bar business, he needs to look at what has been called a critical date, which is a year before.

And I'm not going to allow Dr. Fruehauf to be

instructed on whether publicly available information for purposes of the on-sale bar is all a POSA is assumed to know. So, if you would like to continue to inquire, please feel free to do so, but make your question clear to him.

MR. O'MALLEY: Sure.

BY MR. O'MALLEY:

Q. Now, let me build on the judge's observation.

With respect to the notion -- you've reviewed -- let me back up -- Dr. Saab's and Dr. Peck's report.

A. Yes.

Q. And you have reviewed their opinions relating to whether a person of ordinary skill reviewing the patent description and disclosure as of the date the patent was filed would believe the inventors to be in possession of the invention.

Do you recall that?

A. Yes.

Q. And, so, you're aware that the focus on that analysis is on the date the patent application is filed, correct?

A. Yes.

Q. Okay. Now, with respect to this -- you've also seen testimony relating to whether the patent-in-suit was on sale; is that correct?

A. Yes.

THE COURT: Opinions, you mean.

MR. O'MALLEY: Opinions.

BY MR. O'MALLEY:

Q. And you're aware that focus for that analysis is one year prior to the patent application date, correct?

A. I believe I heard testimony to that effect on Tuesday.

Q. Okay. Now, in terms of our case, you're aware that some significant information enters the public domain regarding the status of Helsinn's development efforts in that one-year period between the critical date and the filing dates of the patents, correct?

A. I'm not sure what information you're speaking of that reached the public domain.

Q. Sure. Let's turn to PTX-0297.

And, again, it's in your -- it's in your notebook. You can look at as much as you like. And you've seen that document before?

A. I don't recall.

Q. Why don't we turn to the conclusion section at the bottom of the chart.

Do you recall us reviewing this publication at your deposition?

A. I don't recall, but I'll accept your assertion.

Q. Okay. And you see the date of this publication if we go back to the first page, June 23 to 26, 2002.

Do you see that?

A. Yes, yes.

THE COURT: Is this a paper presented at that meeting, conference?

MR. O'MALLEY: Well, perhaps I should ask the question.

BY MR. O'MALLEY:

Q. You understand this to be an abstract?

A. It says "oral presentation."

Q. Okay. And what form of publication is this, to your understanding?

A. I guess the -- there may be a journal of the Multi-National Association of Supportive Care In Cancer.

Q. Okay.

A. Usually they will publish a proceedings for their journal, which would include abstracts from the national meeting. And while the oral presentation is not included in the publication, the abstract is included in the publication.

Q. And you understand that an abstract like this would be publicly available in this case prior to the filing date of the '219 patent?

A. Yes, sir.

Q. Okay. And then if we look at the conclusions -- well, first of all, if we blow up the box above the conclusions.

Now, you recall or perhaps you now note that this MASCC abstract reports some Phase III clinical data for palonosetron with respect to CINV?

A. These data look to me to be from 99-04.
Q. Okay. And you understand that to be Phase III clinical data for palonosetron with respect to treatment of CINV.
A. Yes.
Q. And you see that there is some treatment rate reported there?
A. Yes.
Q. And for the .25, the acute response is 63 percent.
Do you see that?
A. The -- that would be the complete response in the acute phase.
Q. Yes.
A. Of 63 percent control.
Q. Right. And there is data for complete response in the delayed phase, 24 to 120 hours.
Do you see that?
A. Yes, sir.
Q. And for .25 milligrams, there's a response rate report of 54 percent?
A. Yes.
Q. And do you see that --
THE COURT: The comparator is different in that 04 Phase III study, isn't it?
THE WITNESS: It was dolasetron here, and it was dolasetron was --

THE COURT: At 100 milligrams.
THE WITNESS: At 100 milligrams.
THE COURT: Okay. Fine.
THE WITNESS: So it's a setron that was less potent than ondansetron.
BY MR. O'MALLEY:
Q. Now, if we go to the conclusion, it states, "Palonosetron has demonstrated significant activity in preventing both acute and delayed emesis with a single I.V. dose. In patients receiving moderately emetogenic chemotherapy, palonosetron was safe and well tolerated."
Do you see that?
A. Yes, I do.
Q. And you agree that the data supports that conclusion, correct?
A. Yes.
Q. Now, in your opening report, you stated -- and if you don't recall this, we'll put it in front of you -- "Phase II trials are designed to assess and establish an indication of clinical efficacy of the drug compound for treating particular disease conditions or symptoms," correct?
A. I'm not sure if those are the exact words, but --
Q. Well, why don't we pull up DTX-1179-0010, Paragraph 23. And we've highlighted the words, and let me just read that into the record, and I'll finish the sentence for

completeness: "Phase II trials are designed to assess and establish an indication of clinical efficacy of the drug compound for treating particular disease conditions or symptoms, and includes finding the minimum effective dose of the drug."

Do you see that?

A. Yes, sir.

Q. And you were in the courtroom when Dr. Calderari testified?

A. Yes.

Q. And you heard that he called it -- he referred to it as a signal of efficacy.

Do you recall that?

A. Yes. That's a pharma -- pharmaceutical company jargon.

Q. Okay. And indication of clinical efficacy, does that mean something different than Dr. Calderari's signal? I believe in your direct testimony, you likened the two terms.

A. I agree.

Q. Okay. Now, you provided some opinions regarding 2330, the Helsinn's -- well, Syntex's Phase II study, correct?

A. Yes.

Q. And Study 2330 reported data as you noted for a 3-microgram-per-kilogram dose, correct?

A. Yes.

Q. And that corresponds to roughly a .21-milligram total

dose; is that correct?
A. Yes. I think that we were sort of rounding it to the .25.
Q. Fine. I'm making no distinction.
The study also reported data on other doses, correct?
A. Yes, it did.
Q. There was the .3- to 1-microgram-per-kilogram dose, correct?
A. Well, those were separate doses, but those doses were combined into one category.
Q. Right.
A. So, there's that one category of the lower doses combined together.
Q. And those lower doses combined together were considered the control in the study.
Do you understand that?
A. I believe that was the intent.
Q. Okay. And then there was a number of other doses, 1 microgram per kilogram, correct?
A. Point -- it was .3 to 1 was the low dose.
Q. I'm sorry. I didn't mean this to be a memory test. Why don't we get it up there. DTX-0227-0015.
And let's highlight the summary and conclusions and down through the chart and footnote.
So, the other doses studied besides what was intended

to be the control, as you put it, were the 3 microgram per kilogram, correct?

A. Yes.

Q. The 10 microgram per kilogram?

A. Yes.

Q. The 30 microgram per kilogram, and the 90 microgram per kilogram?

A. Yes, sir.

Q. Now, if you look at the summary and conclusions, it concludes that "All four doses were approximately equally effective as compared with the combined results from a cohort of .3 and 1 microgram per kilogram."

Do you see that?

A. Yes.

Q. And that phrase "cohort" is -- refers to what you mean they combine the data from doses in that range?

A. Yes, sir.

Q. Okay. And then it has the table.

Now, underneath the table, there is an indication of an asterisk and with respect to statistically significant differences p less than .05 versus lowest dose group.

Do you see that?

A. Yes, I do.

Q. And you provided a brief explanation of what this -- what do we call the p-value in statistics, again?

A. The probability that an event could occur by chance alone.
Q. Right. And this -- this designation under the chart that regarded statistically significant differences is only those differences that had a P less than .05. That's rather standard in the pharmaceutical industry. You know that?
A. Yes, it's an arbitrary choice.
Q. But it's standard, correct?
A. It -- it is a standard.
Q. Yes.
Now, with respect to the results for complete control after 23 -- 24 hours, rather, you see there's a value of 24 for the cohort of .3 to 1?
Do you see that?
A. Yes.
Q. And do you see the value for 3 microgram per kilogram is 46?
A. Yes.
Q. But you recognize that there's no asterisk next to the 46?
A. Correct.
Q. And according to the authors of this study, that means there was no statistically significant difference between that value for complete control at 24 hours and the value for the cohort, correct?

A. That is correct from a statistical perspective.
Q. Okay. Now, in fact --
THE COURT: Is there an asterisk on some of those hour figures down on the bottom row? But not otherwise.
THE WITNESS: Yes, that's right. 22.7 has the asterisk for the time to failure, so that was statistically significantly different for the .25 compared to the .3 to 1.
BY MR. O'MALLEY:
Q. Now, in reviewing these clinical trials, you're familiar with the notion of a primary endpoint.
A. Yes, sir.
Q. And can you explain to the judge what primary endpoint means?
A. The primary endpoint would be the endpoint around which you design your trial.
Q. And in this case and in the case of these other clinical trials you've testified about today, the primary endpoint is percent complete control, correct?
A. Yes.
Q. Now, with respect to that primary endpoint, the only value that showed statistically significant difference compared to the lowest cohort was the value at 30 microgram per kilogram, correct?
A. Yes.
Q. And that's roughly a 2.1-milligram dose roughly; do you

agree with that?
A. Yes.
Q. Now, you're aware that in general the FDA will not allow you to claim an indication if you do not show statistical significance for an outcome for a primary endpoint in the study. You're aware of that, correct?
A. Yes.
THE COURT: Could I just interpose one question, please?
MR. O'MALLEY: Certainly.
THE COURT: Just looking at our column for the 3-microgram dosage, and it says 46 percent --
THE WITNESS: Yes, ma'am.
THE COURT: -- complete control in the first 24 hours. This is 46 percent of the people tested reported complete control; is that what it's telling us?
THE WITNESS: 46 percent of the people who got the drug --
THE COURT: Right.
THE WITNESS: -- had complete control compared to 24 percent of the patients who got only .3 to 1, and I had testified earlier that you can imagine there's people that would get nothing. There's zero.
THE COURT: Right.
THE WITNESS: But here we're comparing 3 to .3 to 1,

where there's some benefit from the .3 to 1, and -- but they combine that data just to have some comparator, but it may come out later what was actually asked for.

THE COURT: No, the direction of my question was just that that number, 46, is percentage of patients receiving the particular drug at that dosage who exhibited or reported complete control --

THE WITNESS: Yes, ma'am.

THE COURT: -- of their symptoms.

THE WITNESS: Yes, ma'am.

THE COURT: So, no nausea.

THE WITNESS: No nausea and no need for rescue medication.

THE COURT: Okay. If they were, like, you know, better, but not greater on the nausea scale, they didn't make it into the 46 percent, right?

THE WITNESS: Correct. They could have had a benefit, but it wouldn't have been to the degree that was required for this analysis.

THE COURT: Okay.

BY MR. O'MALLEY:

Q. Now, you're aware, Dr. Fruehauf, that the FDA concluded that study 2330 did not establish efficacy, correct?

A. My opinion on that question --

Q. I didn't ask your opinion on that question.

A. But it has to do with the context of what their decision was.
Q. Are you aware that the FDA concluded that; yes or no?
A. Eventually, they did conclude that it was.
Q. Eventually they --
A. That's why they allowed it to go to the Phase II -- Phase III.
Q. Dr. Fruehauf, let me ask my question again. Are you aware that the FDA concluded that the Study 2330 did not establish efficacy?
A. There were various communications with the FDA about whether the .25 dose was correct as being the minimally effective dose.
Q. Now, let me pull up the transcript at Page 165:17 to 165:5.

"QUESTION: Now, are you aware" --

THE COURT: What transcript are you reading from?

MR. O'MALLEY: Dr. Fruehauf's transcript.

THE COURT: Deposition?

MR. O'MALLEY: Deposition transcript, thank you.

BY MR. O'MALLEY:
Q. And I passed up a copy of that.

"QUESTION: Are you aware that the FDA concluded in reviewing this data that it could not be used as evidence of efficacy because of a lack of dose response?

"ANSWER: You know, I've heard that -- I've seen that. And I think that, you know, I did work closely with the FDA when I was at NCI as a fellow and CBER and those people. I even imagined at one time that I might even work in the FDA. And, you know, those are human beings, just like the patent reviewer people are human beings, and they can make mistakes."

Did I read that correctly?

MR. WONG: Objection, Your Honor. That's not impeachment.

THE COURT: He can ask whether this has been read correctly, Mr. Wong.

BY MR. O'MALLEY:

Q. Did I read that correctly?

A. That's read correct.

MR. O'MALLEY: Let's pull up PTX-0261, Page 5, and let's go down to --

THE COURT: Now, what is this?

MR. O'MALLEY: Let's go to the cover page of this.

BY MR. O'MALLEY:

Q. And do you recall that Dr. Calderari presented some testimony regarding this document during his testimony?

A. Yes, sir.

Q. And do you recall that this was described by him as an end of Phase II meeting minutes?

A. Yes, sir.

Q. And that the meeting minutes were prepared by the FDA?
A. Yes, sir.
Q. And the date of this is March 10, 1999.
Do you see that?
A. Yes, sir.
Q. And Dr. Calderari testified that he attended that meeting, correct?
A. Yes, sir.
Q. Now, if you go down to Page 0005 in Question 6, and you understand that the format of this document is that the pharmaceutical company poses certain questions at the meeting in the minutes with the highlighted bullet points are meant to summarize the FDA's response to those questions?
A. Yes, sir.
Q. Okay. And in Question 6 Helsinn asked, "Is 2330 sufficient to support the label claim 'including high-dose Cisplatin' should a historical control analysis be conducted?"
Do you see that?
A. Yes, sir.
Q. And I'll skip down to the bullet: "Due to the lack of a dose response in this study, these data are inadequate to serve as pivotal efficacy support (although they may be useful as supportive data)."
Do you see that?
A. Yes, sir.

Q. Now, when we discussed this at your deposition, do you believe -- do you recall telling me that you believed the FDA was wrong?
A. Well --
Q. Yes or no; do you recall that?
A. Yes.
Q. Okay.
A. But that was in a different context.
Q. I see.

Now, are you aware that Helsinn was asked to reanalyze Study 2330 by the FDA?
A. Yes.
Q. Now, in discussing why you thought the FDA was wrong in specific to this conclusion, you testified that "I would think if they were pharmacologists, they would have come to a different conclusion or they didn't look at all the data correctly."

Do you recall providing that testimony?
A. Yes.
Q. And, again, you've never been personally involved in the selection of a specific dosage of a drug in a treatment that was eventually approved by the FDA, correct?
A. Yes.
Q. Now, let's look at -- you cited to the August Consulting letter, DTX-0293. Can we pull that up?

Do you recall providing testimony about that document in your --

A. Yes, sir.

Q. -- direct testimony?

A. Yes, sir.

Q. Do you need -- okay. You got some water.

Turning to Page 30 in the document, the last line of the third paragraph reads -- if we can highlight that, Roy -- "Results achieved in Phase II CINV studies suggest that palonosetron is safe and effective in preventing nausea and vomiting following emetogenic chemotherapy, especially during the 24 hours after administration."

Now, the word "suggest" as you interpret it from your POSA in the clinical sciences standpoint, is that the same thing, does that have the same meaning as "signal" or "indication" as we discussed before, suggestion?

A. It has the meaning of probability from the standpoint of that it's likely to reduce the risk, and likely to reduce the risk is not a statistical assertion, so likely to reduce the risk/suggest go together, likely and suggest.

Q. Now, looking further down to the last line of the page, it states that "This study is designed to support the hypotheses that palonosetron is not inferior to currently available 5-HT_3 receptor antagonists and is effective in preventing nausea and vomiting following moderately emetogenic

chemotherapy."

The study they're referring to, again, is Study 2330. Do you understand that?

A. They've referred to it in the past tense already. It said, "Given the high affinity and efficacy results in both end walls in Phase II" --

Q. Yeah, and, by the way, why don't I interrupt you because I misspoke. This is referring to study, as you testified, 99-03, correct?

A. Right. It's not for the Phase II study.

Q. Yeah. And, so, you agree that this is an accurate description of the hypotheses that Study 99-03 was designed to test?

A. Yes, 99-03 was designed to test a noninferiority endpoint.

Q. And you understand in order to get a MEC indication from the FDA, they needed an additional study, 99-04 in addition to this noninferiority study, 99-03, correct?

A. Um, I don't know what the FDA told them as to what would be required for approval.

Q. You're not aware that that was an agreed-upon requirement between Helsinn and the FDA?

A. No. I know that they went and they had their meeting and they discussed all three trials, three studies.

Q. But are you aware then in order to get an indication for

MEC, they had to have a successful showing not only in 99-03, the noninferiority study, but, also, in 99-04?

A. You know, as to what would happen after the results of those trials are in and when they filed or for an NDA, it's hard to say; but I think the pre-IND meeting that they had, that the FDA is telling them, gee, if you do a good job on these studies, you have a high likelihood of getting approval.

Q. So, you don't understand that prior to Phase III, there was an agreement at that time between Helsinn and the FDA that they would need to show a successful outcome, not only in 99-03 for MEC, but, also, 99-04 for MEC; you don't understand that?

A. No, I understand that, you know, they tried to get, you know -- they tried use the Phase II study as the pivotal study. That was the prior discussion we had.

They didn't allow them to use it as the pivotal study for purposes of approval, so they said if you want approval, you need to do pivotal studies, and they told them to do --

THE COURT: Before Phase III?

THE WITNESS: They tried to -- the prior discussion was related to trying to use the Phase II study as the labeling study.

THE COURT: Don't you always have to do Phase III studies?

THE WITNESS: Not always. But because they did this

prospective, randomized, double-blinded Phase II study, but they were told no, you didn't get this right, you didn't get that right, you need to go forward and do Phase III studies.

BY MR. O'MALLEY:

Q. My question is more specific, and if you can't answer it, just please tell me and I'll move on.

Did you understand that prior to Phase III that Helsinn understood, and the FDA had so told them, that in order to get an indication for MEC, they had to have a successful outcome out of both 99-03 and 99-04?

A. For moderately emetogenic chemotherapy --

Q. Yes.

A. For moderately emetogenic chemotherapy --

Q. Okay.

A. -- because that was the key, was the indication was moderately emetogenic chemotherapy.

Q. Correct, and to get an indication for HEC, highly emetogenic chemotherapy, they needed, one, to reanalyze the 2330 Study and get a successful outcome in 99-05.

Do you understand that?

A. Yes. They were going to allow them to use the Phase II study as supportive data, so they really only needed one Phase III trial for highly emetogenic chemotherapy and then based on the Phase II study and the Phase III, they would approve it for that indication.

THE COURT: But they did have to reanalyze the Phase II HEC data --

THE WITNESS: And that's what --

THE COURT: -- is that right?

THE WITNESS: Yes, because I was, you know saying earlier, you can imagine if you had no treatment. So they went back and they put in a sort of like if it was a placebo category of historical controls, and then they reran their statistical analysis, and now it was significant.

BY MR. O'MALLEY:

Q. But it wasn't before in the FDA's eyes, in any event?

A. No. It wasn't adequate for labeling at that time. That's really the distinction. In other words, the context was they didn't feel it was adequate for labeling at that time.

Q. Now, let's turn to the Formulation Book DTX-0254.

And you've reviewed this book before?

A. I don't remember seeing the Formulations Book.

Q. I'm sorry?

A. I don't remember seeing the Formulation Book. I knew it was discussed at the -- I know it was previously discussed. I can't remember looking at it.

Q. Okay. Are you aware, and we can go through it if we need to, that as a result of its analysis or analyses of the Phase II study, 2330, that Roche/Syntex recommended a dose for Phase

III clinical trials for CINV of 1 milligram?
A. This is May 1995?
Q. This publication is, yeah.
A. So, you're referring to this publication?
Q. My question is more general.
Are you aware that Roche/Syntex made that recommendation based on its analyses of Study 2330?
A. At what time?
Q. At any time.
A. I don't remember seeing that --
Q. So you're not aware --
A. -- in the material I read.
Q. You're not aware of that?
A. I'm not aware of that.
Q. Why are you focusing on the time frame in this question?
A. I was trying to understand what the Formulation Book is. I don't know this and how that would relate to clinical trials' outcomes.
Q. Are you aware of when 2330 was finalized?
A. I thought it was June of 1995.
MR. O'MALLEY: Okay. And in that, why don't -- can we pull out 2330. And find the signature page. Likely around the last page, Roy.
BY MR. O'MALLEY:
Q. Now, while he's looking for that, with respect to the

date that the final report is signed, that's a date that you have in mind? Whether it's accurate or not, you're thinking of the date the final report was signed?

A. Yeah, I mean, I'm thinking about it would be difficult to reach a conclusion without knowing the 2330 data about what dose should go forward, and you need to go through a whole lot of different processes, so July 1995.

Q. Do you recognize this to be the final report for 2330?

A. Yes. And the report is July 1995.

Q. And let's go to the last page.

And you see it was signed even after that in September of 1995?

A. Yes.

Q. Now, are you aware the Formulation Book discusses the results of Study 2330?

A. No.

Q. No. But you are aware that results are available, that seemed to be a theme of your testimony this morning, before the final report on any given study is both prepared and signed, correct?

A. Now this Phase II study would be much more difficult to try and do an analysis on blinded data, if that's what you're alluding to.

Q. No, I'm just saying before the final study report is executed and signed, often results are available, preliminary

may they be, correct?
A. I don't know when the, you know, data analysis were done. I just -- what I'm saying is, to me, the company prepared this report and finally signed it in September of 1995, and you're showing me a book from May. So I don't know what the connection is between who was writing these different things and what they were referring to and thinking about when they wrote them.
Q. But, in any event, you're not aware that Roche/Syntex made a recommendation based on its review of Study 2330 that Phase III trials employ 1 milligram total dose in CINV?
A. I'm not aware of that.
Q. Okay.
A. I'm not aware of that.
Q. Let's turn to DTX-1023.
Now, in your expert report, you discuss the fact that you reviewed Dr. Candiotti's expert reports and exhibits. Do you believe that?
A. Candiotti?
Q. Candiotti.
A. Yes.
Q. And do you recall this was one of Dr. Candiotti's exhibits?
A. I don't remember, but I'll say yes, I mean.
Q. Okay. Now, this is a letter dated January 7, 1998 from

Kathleen Lee.

Do you see that?

A. Yes.

Q. And you are aware Dr. Lee is listed as one of the inventors on the face of the patents-in-suit?

A. Okay. Yes.

Q. And you were here when Dr. Calderari testified that she was formerly, before this date of this document, affiliated with Roche Palo Alto, which was formerly Syntex, correct?

A. Yes.

Q. And you heard that Dr. Lee oversaw Phase II palonosetron clinical studies while at Syntex?

A. Yes.

Q. Now, if you turn to the first page of this document and the first sentence of the third paragraph, it states, "The RS-25259-197 program was halted by Roche following completion of clinical Phase II studies."

Have you heard testimony about that?

A. Yes.

Q. Now, are you aware that prior to terminating the palonosetron project, I know you said you weren't aware of the specific dose, but are you aware that Roche did, in fact, determine a dosage of palonosetron to carry forward to the clinical studies?

A. I'm not aware of that.

Q. Could you turn to the second page, the table?
And specifically let's turn to 003, and do you see a product definition?
A. Yes.
Q. And Table 2 is entitled, "Developmental Assumptions"?
A. Yes.
Q. And do you see that with respect to the CINE dose that's defined here, the total dose is 1 milligram?
A. Yes.
Q. Now, are you aware of any evidence in the documents you've reviewed whereby Roche/Syntex recommended a dose other than 1 milligram for Phase III CINV?
A. So, I'm understanding, this is Dr. Lee's letter from a third party now. She doesn't work for Roche or Syntex or --
Q. My question has nothing to do with the letter at this point.
A. I'm just trying to understand what we just looked at.
Q. My question to you is are you aware of any documents, yes or no, whereby Roche/Syntex recommends a dose other than 1 milligram for Phase III clinical trials?
A. I said I wasn't really aware that they recommended the 1-milligram dose. I don't know about other doses.
Q. So, your answer is you're not aware?
A. The only thing I'm aware of of what Syntex was saying was their participation in the meeting with Helsinn, where the

Syntex people that were there cooperated with Helsinn, and what the conclusions of that joint Syntex/Helsinn meeting those conclusions were. And we saw from my testimony earlier, it was .25 and .75.

That's the only knowledge I have about the interaction between Syntex people and Helsinn people on dose selection.

Q. Well, to be accurate in that document, it was .25, .75, and 2 milligrams.

A. Correct. I correct myself. There was also a 2-milligram recommendation, but there was not a 1-milligram recommendation.

Q. Let's look at Roche 7739 to 7742. Have you seen this document before?

A. No, I have not.

Q. Now, I'm just going to -- and you understand that Roche Bioscience was by this time a division of Syntex U.S.A.?

A. Gosh, I thought Syntex was a division of Roche.

Q. So, you're not aware who Roche Bioscience is?

A. I mean, Roche, I believed, acquired Syntex.

THE COURT: Maybe Roche Bioscience is actually a sub under Syntex and Roche --

THE WITNESS: Okay. So, I see. So they just transferred their -- so they have two layers and Syntex is in between maybe.

THE COURT: I don't know.

Counsel, what's the date of this?

MR. O'MALLEY: The date of this is 18 October 1995.

BY MR. O'MALLEY:

Q. Do you see that, sir?

A. Yes, I do.

Q. And are you aware by this time Roche had decided to discontinue the palonosetron product?

A. I'll accept that.

Q. And are you aware that during this period of time, Roche was looking to out-license palonosetron to a different pharmaceutical company?

A. Okay.

Q. And do you see this as a communication to Bristol-Myers Squibb?

Do you see that?

A. Yes.

Q. And on the second page of this document, there's an outline of Draft 3 of Draft Phase III Protocol.

Do you see that?

A. Yes.

Q. And under study medications it states, "RS-25259: Based on the Phase II study results, it is expected that a dose of 1 milligram I.V. RS-25259 will be effective."

Do you see that?

A. Yes, I do.

Q. And you've not seen this before, I take it?
A. No.
Q. Now, you referred to a meeting that involves some Syntex scientists. Was that your 1998 meeting minutes you had in mind?
A. Yes, sir.
Q. Why don't we turn to that, PTX-0015.
Now, again, you don't have any basis for believing this document was publicly available, correct?
A. I don't know that.
Q. You don't know --
A. I don't know that it was publicly available or not.
Q. Any reason to believe it is?
A. No.
Q. Do you see in the upper left-hand corner, it says "confidential"?
A. Yes.
Q. Now, it appears that these are minutes from a series of meetings that took place that day?
A. Yes.
Q. And I believe you were referring to -- well, let me ask you: In your prior testimony, were you referring to DTX-15-0008, the minutes of the clinical meeting?
A. DTX-0015.
Q. 0015-0008. In any event --

A. Yes.
Q. -- is this the page you were referring to?
A. Correct. Yes, sir.
Q. Okay. And I believe you directed our attention this morning to testimony regarding the CINV proposed doses?
A. Yes, sir.
Q. And at this point in time among Helsinn internally, the recommendation was still to keep 2 milligrams as one of the Phase III doses.
Do you see that?
A. Yes. Not the 1 milligram, but a different one than they were, I guess, thinking about earlier. They've switched from 1 to 2 now, but they brought in the .25 and the .75 after reanalysis of the data with other people from the outside.
Q. Sir, do you see that?
A. Yes, I see that.
Q. Okay. That's all I'm asking you is --
A. Yes, sir.
Q. -- yes-or-no questions. Your counsel's going to get a chance to let you pontificate.
A. My apologies.
Q. Now, that 2.1 -- 2.0-milligram dose, that's equivalent to 30 microgram per kilogram, correct?
A. Yes, sir.
Q. And you recall when we looked at 2330, the 30 microgram

per kilogram was the only dose that showed statistically significant difference relative to that cohort, correct?

A. For the 24-hour --

Q. For the primary endpoint.

A. -- complete control. Yes.

Q. Yes.

Now, do you recall Dr. Calderari's testimony to the effect that his clinical colleagues were lobbying to test a higher dose than they eventually tested in Phase III clinical trials?

A. I don't remember that, but I'll accept that.

Q. And that he had a concern, based on this balancing, between efficacy and stability.

Do you recall that testimony?

A. I do remember that. That went to the -- okay. Yes.

Q. And, so, based on his concerns about that balance and how many doses it was practical for Helsinn to take into Phase III, they decided that they could not take the 2-milligram dose into Phase III.

Do you recall that generally?

A. No, but I'll accept that.

Q. Okay. Now, if you turn to the next page of the clinical meeting minutes, and specifically under CINE dosing, the minutes from that meeting of the clinical team included a conclusion that "In a review of the study data, the

3-microgram-per-kilogram dose may not be the most effective."

Do you see that?

A. Yes, I do.

MR. O'MALLEY: I'm not really keeping track of time, your Honor, so I assume you'll tell me if we get to where you want to break.

THE COURT: You read my mind.

MR. O'MALLEY: Okay. Then I'm at a stopping point, so we can break here.

THE COURT: Perfect. Thank you. We'll take a little recess.

(Brief Recess.)

THE COURT: Continue.

BY MR. O'MALLEY:

Q. I would like to turn to DTX-0287-0413. And this is a declaration you provided testimony about in the morning. Do you recall that?

A. Yes, sir.

Q. And for shortness, I'm just going to refer to that periodically as the Cantoreggi declaration. Is that okay?

A. Yes, sir.

Q. Now, this is a declaration on -- given by Sergio Cantoreggi, Enrico Braglia, and Riccardo Braglia. Do you see that on the first line?

A. Yes, I do.

Q. I'm sorry?
A. Yes, I do.
Q. Okay. And then it states that, in Paragraph 3, "In particular, we submit this declaration to establish that Alberto Macciocchi" -- and I'm mispronouncing that and my client will please forgive me -- "Enrico Braglia and Riccardo Braglia, had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV, and had conducted clinical trials in humans to test this idea, at least as early as October 2, 2001." Do you see that?
A. Yes, I do.
Q. And although Sergio Cantoreggi is one of the declarants, there is no assertion in here that he was part of the conception of the idea to use palonosetron for treatment of CINV, correct?
A. Correct.
Q. Now, going back to Paragraph 2, it says, "We submit this declaration to establish that Alberto Macciocchi, Enrico Braglia, and Riccardo Braglia had conceived the invention defined by claim one of this application, and reduced it to practice, before November 16, 2001, the date that Dr. Piraccini published abstract Number 5169 in Blood, Volume 98, No. 11 Part 2." Do you see that?
A. Yes, sir.
Q. What does "reduced to practice" mean?

A. I'm not an attorney. I would not want to take a stab at that. If there was a clinical thing, to me, it means you're, you know, doing something for patients, but this is a patent question.

Q. It's a legal term.

A. It's a legal term.

Q. And you're an American, correct? You live in California.

A. Yes, sir.

Q. Indeed, you're an inventor on a number of United States patents, correct?

A. Yes, sir.

Q. But you're not clear on what the term "reduced to practice" means. As you put it, it's a legal term.

A. It's a legal term.

Q. Yeah. Now, you understand that the declarants of this declaration are Italian speaking?

THE COURT: You can assume that.

THE WITNESS: I assume that.

BY MR. O'MALLEY:

Q. Okay. And are you aware that these patents relating to palonosetron were either their first patents ever or among their first United States patents ever? Are you aware of that?

A. No.

Q. Have you seen any testimony from any of the declarants in

this case?

THE COURT: Any of these folks, the four of them?

BY MR. O'MALLEY:

Q. The declarants, Sergio Cantoreggi, Enrico Braglia or Riccardo Braglia, have you seen any testimony from them in this litigation?

A. Was it Sergio Cantoreggi here on Tuesday? No. That was -- that's a different person.

THE COURT: Calderari.

THE WITNESS: Calderari. I'm confusing the Italian names. So no, I don't believe I've ever seen them give testimony.

BY MR. O'MALLEY:

Q. Okay. So, you have no basis for knowing or speculating how they interpreted this legal term, "reduced to practice," correct?

A. No, sir.

Q. Now, if you turn to Paragraph 9, it says, "Enrico Braglia and Riccardo Braglia worked with Dr. Macciocchi as he developed the clinical protocol for PALO-99-03," and it goes on from there. As you read that sentence, the "he" clearly refers to Dr. Macciocchi?

A. Yes.

Q. Now, nowhere in this declaration does it assert that the Braglia brothers, and I'll call them that for short, were

personally involved in any aspect of PALO-99-03, other than working with the person who developed the clinical protocol, correct?

A. Yes. I don't know how to interpret this paragraph in terms of what intimate knowledge they would have had in the process.

Q. But there is no assertion that they were personally involved in these clinical studies, correct?

A. Just says they worked with him as he developed the clinical protocol.

Q. Now, you've -- are you aware that the Braglia brothers in the time period when palonosetron was being developed were co-CEOs of the company? Do you recall Dr. Calderari's testimony to that effect?

A. I remember there was a time I think their father ran the company and they worked for him and -- but I don't know the dates of --

Q. Okay.

A. -- how the family --

Q. Fair enough.

You've reviewed a number of documents relating to the clinical studies -- meeting minutes, study reports, et cetera. Do you recall the Braglia brothers, either one of them, attending any of these meetings, either with the FDA, with Syntex, et cetera, to discuss these clinical studies?

A. I don't know.
Q. You don't recall that, do you?
A. No.
Q. Okay. Now, there's no assertion in this declaration that Dr. Cantoreggi was personally involved in these clinical studies, correct?
THE COURT: You could show him the portions of the declaration where Dr. Cantoreggi has something attributed to him.
BY MR. O'MALLEY:
Q. Yeah, let me see. Let's go back to Page 1.
Now, the paragraph with respect to Dr. Cantoreggi's connection is, I believe, and the only place I see it is Paragraph 10. It says, "Sergio Cantoreggi has since worked extensively with Palo and is very familiar with the work reported in Palo 99-03." Do you see that?
A. Yes, I do.
Q. And they don't assert the -- whomever drafted this does not assert that Mr. Cantoreggi was personally involved at the time with the work reported in PALO-99-03. Do you see that?
A. Well, Number 4, they're mentioning.
Q. I'm sorry?
A. Number 4.
Q. Number 4, let me see what you're -- let's pull up Number 4. And what are you -- why are you citing that to me?

A. Well, Sergio Cantoreggi is employed by Helsinn, the assignee.
Q. At the time this declaration is signed?
A. Yes. So he was working with the company. That's -- yes, that's what we know.
Q. Do you have any basis for knowing that Dr. Cantoreggi was involved with the clinical trials while they were being undertaken?
A. I don't really know what their management structure was or how they organized their --
Q. You don't know one way or the other?
A. No, sir, not one way or the other.
Q. When you were listening to Dr. Calderari's testimony, do you recall him testifying that Dr. Cantoreggi, in the time period when palonosetron was being developed, worked in the toxicology lab?
A. I don't remember that but I'll accept that as true.
Q. Okay. Do you understand that from Helsinn's standpoint in the relevant time period Dr. Macciocchi was in charge of the clinical trials?
A. It's -- it seems to be that way from this document.
Q. And, unfortunately, at the time of this declaration, he had passed away. Do you understand that?
A. No.
Q. Okay. It states it but it's not important enough to go

back.
A. Okay.
Q. Now, you had focused on Paragraph 18 of this declaration. And, as I recall your testimony, you read this to mean that the declarants had seen some indication of success of 99-03 before October 2, 2001. Is that fair? Is that an accurate characterization of your testimony?
A. Yes, it is.
Q. Now, October 2, 2001, is the date the study was completed; is that correct?
A. Yes, sir.
Q. That's --
THE COURT: Last patient out.
THE WITNESS: Yes, ma'am.
MR. O'MALLEY: Last patient out, correct?
THE WITNESS: Yes, sir.
BY MR. O'MALLEY:
Q. And it's sometime before the data is unblinded, correct?
A. Yes, sir.
Q. So, for this statement to have been accurate, according to your interpretation, one or more of the declarants would have had to have determined some signal of success prior to the last patient out, correct?
A. Or at the time of the last patient out.
Q. Well, it actually says "before." Right?

A. Yes.
Q. Okay. So before the last patient was out of the clinic, the way you interpret this paragraph, one or more of the declarants would have had to have done some analysis to see some indication of success of the trial, correct?
A. I think that was really saying that they could have.
Q. They could have?
A. And that could have led to them reaching the conclusion of a successful test.
Q. You say they could have because you don't know, correct?
A. No, I don't know.
Q. So you're speculating.
A. Yes.
Q. Now, you don't know who actually prepared this English language document, I take it?
A. I would imagine an attorney.
Q. Okay. A U.S. Attorney?
A. I don't know.
Q. All right. Now, do you -- are you familiar with the extent to which the three declarants speak English?
A. No.
Q. All right. Do you know whether a translation was prepared for them?
A. I don't know.
Q. Now, in speculating as to how one might see an indication

of success from 99-03 prior to October 2, 2001, you went through some analysis of comparing blinded data to historical efficacy data. Do you recall that?

A. Yes, sir.

Q. Okay. I want to try and understand that in a moment but before I get there, you have no basis to believe that any of the declarants actually did that analysis, correct? Well, I'm sorry, let me rephrase that.

You have not seen any documents or evidence otherwise indicating that, in fact, the declarants had done that analysis, correct?

A. This is the only document that I can look at that suggests that they had successfully tested it, and to make that statement, I was trying to come up with, well, how could you have done that, if the data are blinded, and that's what I did.

Q. So the answer to my question is yes?

A. This is the only -- this document is what I was going by.

Q. Okay. And you've not seen any --

A. Other document.

Q. -- Helsinn documents or other evidence indicating that Helsinn or the declarants ever did the analysis you posited?

A. No, sir.

Q. No, sir, you haven't seen that?

A. No, sir, I haven't seen them.

Q. Okay. I just wanted to understand the "no."
A. Yes, sir.
Q. Okay. Let's take a look at your Fruehauf Demonstrative Slide 9.

Now, you have a 70 percent in the bar, the red bar for historical efficacy of ondansetron; is that correct?
A. Yes, sir.
Q. And you have that drawn lower than the bar that shows 74.4 percent blinded data average for the other three, correct?
A. Well, for ondansetron and the other two.
Q. Yeah.

Now, and you believe it's fair to represent that the 70 percent as being lower than the 74.4 percent?
A. Yes. By 4.4 percent.
Q. Okay. Now, you -- I believe you explained that you obtained that 70 percent historical number from DTX-0288-0064. Do you recall that?
A. Correct.
Q. Okay. But you didn't, as I recall, actually refer to -- bring up the exhibit to show us how you obtained that number. Do you recall that?
A. Yes, sir.
Q. So I want to try and understand that number. If we could pull up DTX-0288-0064. And let's go down to the lower

paragraph, the number of patients.

THE COURT: So this is from the 99-03 Phase III study report? Yes?

MR. O'MALLEY: Can you answer the Judge's question?

THE WITNESS: Yes. 99-03.

MR. O'MALLEY: 99-03. Okay.

BY MR. O'MALLEY:

Q. And I'll represent this was the only place I could find that 70 percent, namely, and the sentence says, "The sample size was based on the assumption of a responder rate of 70 percent in the palonosetron and ondansetron groups and a difference of no more than 15 percent in the complete response rate." Is this the basis for your 70 percent historical evidence?

A. Well, the basis is actually from a prior part, but this is where the number came out because they did the calculations based on the meta-analysis. The meta-analysis is on the prior page.

We looked at 7,000 patients, and I briefly did explain that, but -- so the 70 percent is the number they use for the clinical trial to design the power of the study. They needed --

Q. Now --

A. This is a non-inferiority study.

Q. Now, the 70 percent isn't referred to as a historical

efficacy from ondansetron. There is no designation of that number as historical. Do you see that?

A. Well, you'd have to go back, as I said, to the prior page, at the bottom, where they describe the methods they used to get the 70 percent number.

Q. My question is far easier. At least in this section, it's not described as a historical efficacy number, correct?

A. Because they've already explained how they got it.

Q. Uh-huh.

Now, did you find this number or was it pointed out to you by contrast by counsel?

A. I take personal responsibility for finding this myself.

Q. So you looked through the entirety of the document to glean a historical efficacy number for ondansetron?

A. Well, I wanted to understand the design of the study. And it's a non-inferiority study, so they have to have an assumption of what the comparator will do in the study, and then they have to be non-inferior to that assumption. You can't just do the study and say I'm going to put ten people on each arm and get an answer. You have to have how many people am I going to need in each arm and what will the response rates be of the control group, which is ondansetron. And so they're assuming that the control group, the ondansetron arm, will have a response rate of 70 percent based on the meta-analysis that's described on the prior page.

THE COURT: When you say response rate of 70 percent --

THE WITNESS: Control, control. So they say responder rate there, 70 percent in the sentence. But what responder rate really means is they respond to the drug by having complete control of their -- complete control of the emesis. Complete response is how they refer to it, complete response, so you didn't feel nauseated and you didn't need a rescue medication.

BY MR. O'MALLEY:

Q. Now, let's turn to DTX-0288.0100. And let's look at Table 7.1.1.2. And you understand this is from the same document?

A. Well, that is from the same document, yes.

Q. And the heading says, comparison of complete response, zero to 24 hours, between the ondansetron group and modelled historical ondansetron group. Do you see that?

A. Yes.

Q. And with respect to the data for modelled historical ondansetron, do you see there is a complete response rate stated there of 79.3 percent?

A. Yes.

Q. Now --

THE COURT: And then the next column is the ondansetron dosage and the number of people and the result in

this Phase III, 99-03 study.

THE WITNESS: Yes, ma'am.

THE COURT: Correct? 68.6.

THE WITNESS: 68.6.

BY MR. O'MALLEY:

Q. Now, if we can pull up PTX-075. PTX, the demonstrative. Now, with this demonstrative, we inserted into your form of demonstrative --

A. Um-hum.

Q. -- the number that was listed for the historical ondansetron complete response rate, do you see that, of 79.3 percent?

A. Yes.

Q. And you see that was -- that was about 5 percent greater than the actual response rate for the combined blinded data?

A. Yes.

Q. Do you see that?

A. Yes.

Q. Now, again, you have no basis for believing anyone at Helsinn did this particular analysis that you've described?

A. No. I only -- what we saw that they had stipulated or stated in their patent -- claim --

THE COURT: Declaration.

THE WITNESS: Thank you, declaration -- that they had successfully tested the hypothesis.

BY MR. O'MALLEY:

Q. Now, you began your opinions today that a POSA in the field of clinical science would have known that palonosetron at .25 mgs reduces CINV, correct?

A. Yes.

Q. Now, you did not describe to the Court all of the documents that that POSA would have available to it to judge the efficacy of palonosetron in humans, correct?

A. I'm not sure what all the documents would be.

Q. Well, let's turn to DTX-0276. And you recognize this document, correct?

A. Yes, I do.

Q. And the parties have referred to this throughout the litigation as *Tang 1998*; is that correct?

A. Yes, sir.

Q. Now, as of the critical date, you understand that *Tang 1998* contains the only publicly available, fully peer-reviewed human clinical data regarding the efficacy of palonosetron?

A. Yes.

Q. I'm sorry. Do you understand that?

A. I understand that this was the only prior art that was published for I.V. palonosetron and that it was for an indication of postoperative nausea and vomiting, after hysterectomy.

Q. But my question was a little broader.

As of the critical date, it's actually the only peer-reviewed, publicly available publication containing human efficacy data regarding palonosetron, period, correct?

A. Human efficacy data for postoperative nausea and vomiting.

Q. Of any type.

A. But that's what was studied here.

Q. Of any type.

THE COURT: You mean any type of emesis?

MR. O'MALLEY: Correct. Can you answer that question?

THE WITNESS: It could be. It probably is.

BY MR. O'MALLEY:

Q. Okay. Now, we discussed the fact at your deposition that experts in this case have taken the position that any dose that's effective for CINV for a drug of this class is generally going to be higher than the dose required for PONV, and you weren't able to really take issue with that. Do you recall that?

A. No, I did -- I didn't agree with it.

Q. You didn't -- fair enough. You didn't have any basis to agree or disagree, correct?

A. No, I did. I said that I didn't necessarily agree with it and that there are different doses for different drugs, and you know, for example, ondansetron is used at 16 milligrams

for postoperative nausea and vomiting, and 8 milligrams, half the dose, for chemotherapy-induced nausea and vomiting.

But in my deposition, I said that, you know, there are different doses and different drugs and I didn't -- I wouldn't take that has as a hard-and-fast rule.

Q. Well, I just want to make sure I understand. You have no basis to dispute the general proposition that the approved dosages for treating CINV are generally higher than the approved dosages for PONV for the 5-HT_3s, correct?

THE COURT: Are you just --

THE WITNESS: Are you asking me that question now?

THE COURT: Pardon me, sir.

THE WITNESS: I'm sorry.

THE COURT: You just gave an example?

MR. O'MALLEY: I'm just asking -- I need to know whether he -- I didn't understand his example.

BY MR. O'MALLEY:

Q. Do you have any basis to dispute that?

A. Yes.

Q. All right. Can we pull up the transcript, please, 138:23 and 139:7.

"QUESTION: But my question was simple. Just the approved dosages. Are you aware that for this class of drugs, generally, CINV has higher approved dosages than PONV?

"MR. WONG: Objection.

"THE WITNESS: That may be.

"QUESTION: You have no basis to dispute that?

"ANSWER: I have no basis to dispute it or confirm it."

Did I read that correctly?

A. Yes.

Q. Now, the authors of Tang concluded that with respect to the PONV they studied, only the 30-microgram-per-kilogram dose was effective in reducing postoperative nausea and vomiting. Are you aware of that?

A. I wouldn't agree with that characterization.

Q. Are you aware that they concluded that, whether or not you agree with it?

A. No, they concluded that it was the dose that significantly decreased the incidence of vomiting.

Q. Now, let's go to the abstract. And on the right, beginning towards the bottom, implications. "Implications: RS-25259, a long-acting 5-HT_3 antagonist, was effective in reducing postoperative vomiting only at the largest dose studied, 30 micrograms per kilogram. However, RS-25259 had no antinausea activity, and the larger doses were associated with an increased incidence of headaches in the postoperative period." Do you see that, sir?

A. Yes.

Q. And there is no word "significantly." Do you see that?

A. In that sentence, there is not.

Q. Now, let's go to the -- let's go to DTX-0276-0005. And midway down the page, there is -- at the margin there is a sentence beginning "Only the largest dose." "Only the largest dose of RS-25259, 30-microgram-per-kilogram I.V. was effective in decreasing vomiting and the need for rescue antiemetic drugs during the first 24 hours after major gynecologic surgical procedures." Correct?

A. Yes.

Q. And no use of the word "significantly," correct?

A. Correct.

Q. And right above that, the sentence says that "These results," referring to the summary results, "suggest that smaller doses of RS-25259 are ineffective in preventing PONV." Do you see that?

A. Yes.

Q. Now, in turning to the conclusion, right above the references, "In conclusion, RS-25259, 30-microgram-per-kilogram was effective in preventing PONV in women undergoing major gynecologic surgery. However, it did not decrease postoperative nausea or improve patient satisfaction." Do you see that?

A. Yes.

THE COURT: Just a second, counsel.

PONV, postoperative nausea and vomiting, in one breath they say it's effective in preventing that; then they

say yeah, but not the nausea part.

MR. O'MALLEY: Yeah.

THE COURT: Right, Doctor?

THE WITNESS: Yes, ma'am.

BY MR. O'MALLEY:

Q. Right. And recall, complete response is vomit -- I shouldn't be testifying -- but vomiting or retching; isn't that true, Doctor?

A. Yes, sir.

Q. Okay. And then that secondary indication, you've testified that they often use a questionnaire, how do you feel?

A. Yes. I think they would rather have worded it preventing POV, rather than PONV, and then it wouldn't be confusing. I think that's a misstatement.

Q. Yeah.

Now, nowhere in --

THE COURT: Just a second. In the Phase III trial, 99-03, when you get a complete response figure, as I understood the testimony earlier today, Doctor, complete response includes the questionnaire of the patient, are you experiencing nausea, and they have to say no in order to qualify as complete response.

THE WITNESS: Correct.

THE COURT: In that Phase III trial.

THE WITNESS: Yes.
THE COURT: Okay. Thank you.
MR. O'MALLEY: Okay. Thank you.
BY MR. O'MALLEY:
Q. Now, in -- nowhere else in Tang do they use the word "effective" in connection with any other dosage, correct? Other than 30 microgram per kilogram?
A. Okay. I'll say yes.
Q. Okay. Now, again, to catch us up, 30 microgram per kilogram was the dosage that in Study 2330 was the only dose showing a statistically significant complete response versus the combined control group. Do you recall that?
A. Yes.
Q. And, again, that 30 microgram per kilogram corresponds to 2 milligrams, correct?
A. I believe that's correct.
Q. And then we saw subsequently in the meeting minutes of 1998 involving Helsinn and Syntex people that with respect to the recommendation to go forward in Phase III, at that point in time there was still a recommendation to still use that 2-milligram dose. Do you recall that?
A. Yes.
Q. Now --
THE COURT: But that would be for the CINV, not for the PONV?

MR. O'MALLEY: Yes.
THE WITNESS: Yes, ma'am.
MR. O'MALLEY: Yes. Correct, Your Honor.
BY MR. O'MALLEY:
Q. Now, let's turn to DTX-0264. And let's turn to the 0264.0009, the table of data.
Now, again, you provided testimony about that table, correct?
A. Yes, sir.
Q. And the table is called preliminary data; is that right?
A. It just says, "Table, Summary of Complete Response."
Q. Within the document it's referred to as preliminary data; do you recall that?
A. It may be, yes.
Q. And there were no statistics in connection with this particular preliminary data; is that right?
A. Not in this table.
Q. And there is no safety data presented for these preliminary results; is that correct?
A. Not in this table.
Q. And, again, this is just the preliminary results from 99-03; is that correct?
A. These are the results for what is stated here, which is the complete response proportion in the intent-to-treat cohort.

Q. From Study 99-03, correct?
A. Yes.
Q. And, as you testified previously, in order to get a MEC indication, there would also have to be satisfactory results from 99-04, correct?
A. Well, I mean, I'm not testifying with respect to FDA approval. I'm testifying with respect to the reduction in the risk of nausea and vomiting.
Q. When my question involves indication, my question is -- implicitly involves FDA approval. Do you understand --
A. Oh, okay, yes.
Q. -- to get FDA approval for an indication of MEC, they needed satisfactory results from 99-04?
A. Yes, sir.
Q. Okay. Now, you heard Dr. Calderari testify yesterday that these results just made them hopeful. Did you hear him testify to that?
A. Was that yesterday?
Q. Oh, gosh, I don't know, honestly, if it was yesterday or the day before. But did you hear that testimony?
A. I remember him saying that he was an organic chemist and he wasn't a clinician.
Q. But you heard him say it just made Helsinn hopeful?
A. That these results made them hopeful?
Q. Just made them hopeful, yeah. Do you recall that?

A. No.

THE COURT: Seeing these preliminary results made them hopeful?

MR. O'MALLEY: Made them hopeful.

THE WITNESS: Okay, they were hopeful.

BY MR. O'MALLEY:

Q. But you believe it would demonstrate to a POSA in the clinical science that, in fact, palonosetron would have been known to -- at .25 mgs would have been known by that POSA to reduce CINV, correct?

A. Well, I guess it's possible that since he speaks Swiss-Italian and he's translating into English, we don't know would what the word really means in his mind but it could be that he thinks that he's won, that this is going to be approved based on these results, and that going forward everything is going to be great.

Q. So it's -- in your mind, when he said hopeful, he got the English mixed up; he actually meant "we won" and that's what you believe?

A. I don't know. I don't know what's in his mind and I would say that it's difficult to interpret simply because of the language difficulties.

Q. I see.

You previously testified about a press release from 2000. Do you recall that?

A. Yes, sir.
Q. And do you know that the quote that you cited to was attributed to a Luigi Baroni, Senior Director of Scientific Affairs; do you recall that?
A. Yes, sir.
Q. And do you know anything about his English language capability?
A. No, I do not, sir.
Q. Could we pull up DTX-0040? And let's make that a little bit larger, if we can. And let's scroll up to the date.
And do you see this is January 16, 2002?
A. Yes, sir.
Q. Do you see that date?
A. Um-hum.
Q. Do you see the title is "Helsinn and MGI Pharma announce completion of pivotal Phase III trials of palonosetron"? Do you see that?
A. Yes.
Q. And do you see that this is about a week or so later than the date of the August Consulting letter that attached that table of preliminary results? Do you see that?
A. Yes. Yes.
Q. Now, if you go down to the third paragraph, it states, "We are pleased to have completed all patient treatment and to have begun analysis of the data collected in the palonosetron

3 clinical program," said Luigi Baroni, Senior Director of Scientific Affairs Division at Helsinn. Do you see that?
A. Yes.
Q. And that's pretty accurate in light of the August Consulting letter we saw, correct, as of this moment in time?
A. That they had done the analysis by the date that is on this press release.
Q. Well, strictly speaking, it says, "We have begun the analysis." Do you see that?
A. Yeah, I mean --
Q. Do you see that?
A. Yes.
Q. Okay.
A. They had seen the SAS output. They began the analysis of the data collected.
Q. Begun.
A. Yes.
Q. That's what it says.
A. Yes.
Q. Not finished. Okay.
And then it goes on to say, "The Phase II clinical trial results were promising." Do you see that?
A. Yes.
Q. "And we are hopeful that the Phase III palonosetron data will demonstrate that it can make a difference for cancer

patients suffering from CINV." Correct?
A. Yes.
Q. And this press release was publicly available, just like the 2000 press release, correct?
A. Yes.
Q. I have no further questions.
THE COURT: I would just like to know what this word "pivotal" --
THE WITNESS: Yes, ma'am.
THE COURT: -- that you've been exchanging back and forth means to you, sir.
THE WITNESS: To me, the pharma company -- well, in the drug development process, the pivotal trial is the trial that is what the FDA is looking for to give the NDA license.
THE COURT: Okay.
REDIRECT EXAMINATION BY MR. WONG:
Q. Dr. Fruehauf, Mr. O'Malley began by asking you about your educational training and background in pharmacology.
A. Yes, sir.
Q. Do you recall that?
A. Yes, sir.
Q. When did you get your pharmacology degree?
A. My Ph.D. was in 1996 in pharmacology.
Q. And when did you start that degree?
A. I started that degree in an M.D./Ph.D. program in 1980 --

I started the laboratory part in 1984.
Q. So how many years in total did you spend studying pharmacology?
A. A long time. So from 1984 to 1996.
THE COURT: You got your M.D. what year, sir?
THE WITNESS: 1985.
THE COURT: So you just kept going on this, working on this Ph.D. --
THE WITNESS: (Nods head.)
THE COURT: -- for another decade really.
THE WITNESS: My advisor wanted additional experiments, and so I carried out more experiments as a fellow, and then I carried out experiments after I came to UC Irvine, and eventually, he was satisfied.
THE COURT: And you prevailed.
THE WITNESS: And I prevailed.
BY MR. WONG:
Q. During the course of your career, how many clinical trials have you been involved with?
MR. O'MALLEY: Asked and answered, Your Honor.
THE WITNESS: Yes.
MR. O'MALLEY: In the direct.
MR. WONG: I think the original question was how many clinical trials were you currently involved with.
THE WITNESS: Yes.

MR. WONG: This one is over the course of your career.

THE WITNESS: Yes.

BY MR. WONG:

Q. How many clinical trials have you been involved with?

A. Hundreds.

Q. And your clinical practice at UC Irvine, how long have you had that clinical practice?

A. 1993.

Q. So how long -- how many years?

THE COURT: What year?

THE WITNESS: 1993. So I've been taking care of patients and seeing patients on trials for five years as a fellow at the NCI, and then from 1993 to the present time is 22 years. So 27 years I've been working with patients on clinical trials.

BY MR. WONG:

Q. Okay. And have you been principal investigator on any of those trials?

A. Yes, I have.

Q. How many -- do you recall how many -- how many times you've been a principal investigator on a clinical trial?

A. Well, so, at an institution, the person who's running the study at the institution is the principal investigator, and there are other principal investigators at other places. And

so whoever is running that at an institution is the PI, and so I've been PI on, you know, 50 or 60 trials.

MR. WONG: Let's go back to DTX-0 264. Let's go to Page 9, the Appendix I, the preliminary analysis. Blow up the data, please, on Page 9.

BY MR. WONG:

Q. Dr. Fruehauf, do you recall Mr. O'Malley asking you about the data here?

A. Yes, sir, I do.

Q. Let's start with ondansetron, okay? Is ondansetron effective for reducing CINV in patients?

A. Yes, it is.

Q. And in this data, how many people got ondansetron?

A. 185.

Q. And ondansetron is effective for this indication; is that correct?

A. It's approved for --

Q. This indication?

A. It is approved for chemotherapy-induced nausea and vomiting, and it is approved for postoperative nausea and vomiting.

Q. Okay. So -- and in the zero- to 24-hour row, what percentage of people getting ondansetron had that primary output?

MR. O'MALLEY: I'll just object, it is beyond the

direct. I asked no questions about this table about ondansetron.

THE COURT: I'll permit it.

THE WITNESS: 69 percent. I'm rounding up.

BY MR. WONG:

Q. Now let's go back to palonosetron, 0.25 milligrams. What was the response rate for this dosage form, .25 milligrams?

A. The complete response rate was 81 percent.

Q. And how did that compare to the ondansetron response -- response rate?

A. It's 13 percent better or -- 12 percent better.

Q. And how does that inform your opinions on -- on whether or not the 0.25 milligrams was effective to reduce CINV?

A. I would say that it was not inferior, which is what the study was designed to show; therefore, if it's not inferior, it's at least equivalent; and here, these numbers show it may be a little better.

Q. And for the numbers for palonosetron, 0.25 milligrams, how many patients received that dose?

A. 189.

Q. And so 81 of those 189 patients --

THE COURT: 81 percent.

BY MR. WONG:

Q. 81 percent of those 189 patients had a complete response; is that correct?

A. Yeah, 153 out of the 189 had complete response.
Q. So, based on this data, did 153 people have a reduction in the likelihood of CINV?
A. They certainly did.
Q. Okay. Let's go to DTX-0276, the Tang article. Let me start with this. Is Tang a study on palonosetron for PONV?
A. No, it is not.
Q. I'm sorry. For CINV?
A. I mean, it is not a study for CINV. It is a study for postoperative nausea and vomiting.
Q. And do you have any opinions as to the difference between a study on PONV and a study on CINV?
A. Yes. And I think that I, during my deposition, I explained why it's so different, because you have -- in a postoperative setting, you have the anesthesia, which is the major cause of the nausea and vomiting, and as the anesthesia is leaving the brain, and then you have the pain medications that the patient is given because of the surgery. And, of course, we know that morphine and morphine-type drugs cause nausea and vomiting.

So we have a bunch of things going on in those patients, and it's complicated, and there are a lot of variables in terms of the people that go in the study, what their predisposition is to the anesthesia to cause nausea and vomiting. There's a lot of variables.

Q. And for a CINV study, are there as many variables as there are in a PONV study?
A. It's a little easier. They're not getting pain medication, so you don't have to treat the nausea from the pain medicine. You're really focused on the nausea from the chemotherapy.
THE COURT: And no anesthesia either, right?
THE WITNESS: And no anesthesia.
BY MR. WONG:
Q. So let's look at the actual data in the Tang study. Let's go to 276, Page 4, Table 2.
MR. WONG: Can you blow up -- can you highlight the data for the 3-microgram-per-kilogram dose?
BY MR. WONG:
Q. And this is the .25 milligram dose; is that correct?
A. Yes.
Q. What does this data report?
A. It shows of the 40 people, the percent that vomited within zero to 24 hours was 30 percent, so that would --
THE COURT: The percent that -- that did vomit.
THE WITNESS: Yes.
THE COURT: So this is not a control --
THE WITNESS: So the flip side would be 70 percent control and -- at 24 hours versus 30, 26 percent vomited, so there's a 4 percent difference between the percent that

vomited.
BY MR. WONG:
Q. So in the Tang study, the patients that actually got the 3 mg per kg dose, did they experience a reduction in PONV?
A. Well, if you look at the .1 which is similar to how they did the 2330 analysis in terms of the .1 was the low dose, we'll use that sort of as a control, so 44 percent vomited, versus 30 percent, so 14 percent reduction with the 3, and 26 percent with the 30.
Q. Okay. And let's go to Page 3. Does the Tang reference actually talk about the lower doses and the effectiveness of lower doses? I can point your direction to the left column.
A. Okay. Now I can see it.
Q. About eight lines down, starting with the sentence "Although." Can you read that?
A. Although the need for rescue antiemetics within the first two hours was similar among all groups, 1, 3, 30, -- okay. So, although the need for rescue antiemetics within the first two hours was similar among all groups, 1, 3 and 30 significantly decreased the antiemetic requirement compared with saline within the first 12 hours after surgery.
Q. And the 3-microgram-per-kilogram dose is a 0.25 milligram dose, correct?
A. Correct.
Q. Can we zoom out again, go to the right side, look at

right first paragraph. Can you read the sentence there?
A. Read which sentence?
Q. Sorry. The sentence starting RS-25259, 1.0 micrograms per kilogram.
A. All right. RS-25259, 1 milligram [sic] per kilogram I.V. was also effective in reducing the number of emetic episodes and the need for antiemetic rescue medication within 12 hours compared with saline.
Q. And is that a lower dose than the 3.0-micrograms-per-kilogram dose?
A. That is a lower dose.
Q. So does Tang, the data and descriptions in Tang --
THE COURT: Counsel, I'm not sure you put your question right. I didn't understand it.
MR. WONG: The 1.0 microgram-per-kilogram dose is lower than the dose we're discussing, 3.0, and that's what this sentence is discussing.
Let me ask another question. Maybe that can --
THE COURT: I'm getting the 30 and the 3 in the text -- I can't follow it.
BY MR. WONG:
Q. Okay. Let's go back to Table 2 on the following page. So Tang, the conclusion in Tang only referenced the 30-microgram-per-kilogram dose, is that correct, the one on the right?

A. Yes.
Q. And I'm going to ask about questions on the lower doses --
A. Yes.
Q. -- based on the data in Tang. And the lower doses include the 3-microgram-per-kilogram dose, correct?
A. Yes.
Q. And that's the 0.25 milligram dose that we're talking about?
A. Yes.
Q. Okay. So, based on the data in Tang, as well as the descriptions in Tang, do those data and descriptions tell you anything about the lower doses that were administered in Tang?
A. Yes. So we can see here, the 1 microgram per kilogram, which is one-third of the 3 which is the .25, we come down here, what they're saying is there was a significant decrease for the need for rescue anti-nausea medicines from the zero- to 12-hour point. It was identical pretty much across here for all three doses that the need for an extra pill was reduced by 40 percent. 70 percent of the people that got saline needed that extra pill, but only 43 percent of the people that got the palonosetron at those doses needed an extra rescue pill.
Q. So would a person of ordinary skill in the clinical sciences reading Tang, would they understand that doses less

than 30 micrograms per kilogram showed efficacy for this study?

A. Yes, they would.

Q. Okay. Let's go to the Syntex, let's start at the Syntex 2330 study, and that is DTX-0227. And let's go back to the results on Page 15.

So Mr. O'Malley asked you about the 30-microgram-per-kilogram dose, correct?

A. Yes.

Q. And he pointed out that only that dose had statistical significance, correct?

A. Yes.

MR. O'MALLEY: Objection, mischaracterized the question. But go ahead.

BY MR. WONG:

Q. He pointed out that that dose at percent complete control was statistically --

THE COURT: Can't hear you.

BY MR. WONG:

Q. He pointed out that that dose, 30 micrograms per kilogram, at the percent complete control, 24 hours, was statistically significant, correct?

A. Yes.

Q. And that number is 50 percent, correct?

A. Yes.

Q. The percentage for the three -- the .25 dose is 46 percent, correct?
A. Correct.
Q. Does a difference in 46 and 50 percent affect your opinions as to whether or not the 3-microgram-per-kilogram dose reduces the likelihood of CINV in humans?
A. No.
Q. And why is that?
A. Because it isn't a statistical thing here. It's that we know that this is the plateau, and if you look across at these numbers, there's other points that are significant, and this is just one of them. But that was the primary endpoint, and I think that what -- the questions about statistical significance are really directed to FDA and using this as a pivotal study, and I'm really opining on, did -- was it known that the drug reduced nausea and vomiting at that dose, and it was.

THE COURT: The 3 dose.

THE WITNESS: At the 3. This is a reduction, compared to, you know, only 24 percent had control and, you know, we've talked about, you know, what saline would do. Nobody is going to be controlled.

So I think a person of ordinary skill would look at that 46 and say that that is the lowest effective dose, and I think my testimony substantiates over and over again that in

various documents, they concluded that -- Helsinn concluded that .25 was the minimal effective dose, and FDA agreed with them and allowed them to go forward in Phase III with that minimally effective dose.

BY MR. WONG:

Q. Okay. And so, just to be sure we're clear, the Syntex, Syntex scientists who performed this study concluded that 3 micrograms per kilogram was among the effective doses based on this data; is that correct?

A. Yes, sir.

Q. And you mentioned the FDA -- the meeting minutes with Helsinn. During those meeting minutes, Helsinn also based their decision to go with 3 micrograms per kilogram in the Phase III studies on the Syntex data; is that correct?

A. Absolutely.

Q. And Helsinn also went to then -- went to FDA and made a statement to say that this data clearly demonstrated that 3 micrograms per kilogram was the minimum effective dose; is that correct?

MR. O'MALLEY: Objection, Your Honor. It's become counsel's testimony. These are all leading questions.

THE COURT: I'll let him answer this one and then we'll be done with leading questions.

THE WITNESS: Yes. The FDA, as I said just a minute ago, said, yes, take the .25 forward and .75 forward into the

three pivotal Phase III trials, and so they agreed that .25 was an effective dose to be studied in Phase III.

BY MR. WONG:

Q. And did Helsinn also issue a press release in September, 2000, stating that Phase II studies demonstrated efficacy in emesis?

A. Yes, they did.

Q. Let's go to PTX-2061. Before we get there, let me just take a step back.

Let's go to DTX-0015. These are the 1998 meeting minutes that we reviewed earlier; is that right?

A. Yes, sir.

Q. Okay. Let's go to the portion that Mr. O'Malley referenced to you, Page 9. I think it's right in the middle, CINE dosing.

A. Yes.

Q. And he took you to the first bullet point. Can you read that again?

A. "In a review of the study data, the 3-microgram-per-kilogram dose may not be the most effective."

Q. Okay. Does that say that 3 micrograms per kilogram is not effective?

A. No. It just says it might not be the most effective.

Q. Is that consistent with the Syntex data that the 3-micrograms-per-kilogram dose was among four that they found

to be effective?
A. Yes.
Q. Let's go to PTX-2016. And I think Mr. O'Malley directed your attention to -- okay.
Let's go to DTX number of the same document, DTX-1017. And I think Mr. O'Malley asked you questions on Clinical Question Number 6 that's on Page 6 at the bottom.
THE COURT: This is the FDA and Helsinn meeting?
MR. WONG: Yes, the end of Phase II meeting.
BY MR. WONG:
Q. So Helsinn's questions are at the top; is that correct?
A. Yes.
Q. And is the FDA response below?
A. Yes.
Q. Okay. So can you read -- what is Helsinn asking in Clinical Question Number 6?
A. They want to know if the 2330 can be a pivotal study and use it to get approval. They want to know if it's sufficient to support the labeled claim.
Q. And when it says labeled claim, including high-dose cisplatin, is that for approval?
A. That's for approval.
Q. And what's the second question?
A. "Should a historical control analysis be conducted?"
Q. Okay. And --

THE COURT: What does that mean?

THE WITNESS: That's where we went back and we looked at, you know, how the 99-03, they came up with a historical control number for emesis control for ondansetron.

BY MR. WONG:

Q. And the Clinical Question 6, is Helsinn asking whether the 2330 study is sufficient to support whether palonosetron reduces the likelihood of CINV?

A. No.

Q. And the FDA's response, can you read the first bullet point, starting, "due to the lack"?

A. "Due to the lack of a dose response in this study, these data are inadequate to serve as a pivotal efficacy support, although they may be useful as supportive data."

Q. So what does it mean where FDA is saying for 2330 data is not -- is inadequate to serve as pivotal efficacy support?

A. That they won't get approval just for that one study.

THE COURT: In other words, Phase II is not enough?

THE WITNESS: In this case, this Phase II study was not enough.

THE COURT: Could I just ask, since we're there again, I didn't understand this phrase, "due to the lack of a dose response in this study." What does that mean to you, Doctor?

THE WITNESS: So, I think it did have the dose

response. I think it was just a misunderstanding on the part of the reviewer because --

THE COURT: You mean Phase II had a dose response?

THE WITNESS: Yes, because we saw that the low doses had a low effect. And then the next set of doses were all equivalent. And you just have to --

THE COURT: So there was --

THE WITNESS: So there was an increased effect with a higher dose which is a dose response.

THE COURT: All right. But, still, the FDA was not satisfied with the Phase II.

THE WITNESS: I think that was really -- they weren't going to be -- you know, we don't usually in America, in our FDA, approve studies just on one Phase II study. We usually ask for a little more. But I think that it's interesting that they did allow them, for regulatory purposes, to use it in support of their one Phase III study for highly emetogenic chemotherapy. So it was ultimately --

THE COURT: Whoa, whoa. In support of their one Phase III study for highly emetogenic -- they still had to do a Phase III study for highly emetogenic, didn't they?

THE WITNESS: One. So they only had to do one for highly emetogenic because they were able to use this one as a second study in support of that indication.

THE COURT: Was the Phase II directed to the highly

emetogenic?

THE WITNESS: Yes, ma'am. So this study was done on the highly emetogenic, and it was used in combination with 99-05 for two studies to support the label, whereas 99-03 and 99-04 were two studies for the moderately emetogenic chemotherapy.

BY MR. WONG:

Q. So, just to be clear, is Helsinn asking in this Question 6 whether or not the study, the Phase II study, 2330 alone was sufficient to get approval for a labeled claim including high-dose cisplatin?

A. Yes. So it says, "Is 2330 sufficient to support the labeled claim including high-dose cisplatin?" That was their question.

Q. They wanted to skip Phase III.

MR. O'MALLEY: Leading.

MR. WONG: I'll rephrase.

THE WITNESS: And I think that means they wanted to get approval just on their --

THE COURT: Sustained. You don't have to answer.

THE WITNESS: Okay, sorry.

BY MR. WONG:

Q. Just one last point.

So, at the last bullet point we stopped at, to serve as pivotal efficacy support, but what is stated in the

parentheses?
A. That's what I was saying, that although they may be useful as supportive data -- so the data were good and were ultimately used. Those data were used for approval of the drug for the highly emetogenic indication in combination with the Phase III study.
Q. Okay. Let's go to --
MR. WONG: Can you put up PTX-297? An Exhibit Mr. O'Malley showed.
BY MR. WONG:
Q. Do you remember this abstract that Mr. O'Malley showed you?
A. Yes, I do.
Q. Okay. And let's just confirm the date. What is the publication date of this abstract?
A. Probably June 23rd, 2002.
Q. Okay.
MR. WONG: Let's go to the second page, Page 2. And you can blow up the top.
BY MR. WONG:
Q. Just to confirm, was this for PALO -- was this the study results for PALO-99-04?
A. Yes.
Q. And does the abstract contain only the study data for PALO-99-04?

A. Yes.
Q. Does the abstract contain any other data from any of the other two clinical trials?
A. No.
Q. So, just based on this data alone, for one Phase III trial, would that satisfy your understanding of what Dr. Saab is requiring?
A. No.
Q. Okay. Why is that?
A. Because he said you need two confirmatory Phase III trials.
Q. And --
THE COURT: Well, they had the other one. This paper doesn't say --
THE WITNESS: No.
THE COURT: -- doesn't pull out those results, right, of 99-03?
THE WITNESS: Correct.
BY MR. WONG:
Q. To the best of your understanding, was any other Phase III trial published in the art between 2002 and 2003?
A. No.
Q. Do you recall what the date of completion of the final study report was for PALO-99-04?
A. August, 2002, I believe.

Q. And if we go to the analysis, the section above. So this data was an analysis that was performed prior to the final study report being completed?
A. Yes.
Q. Okay. And --
THE COURT: Which data? Your question refers to --
MR. WONG: The data in this table that is published on --
THE COURT: In that abstract?
MR. WONG: In this abstract.
THE COURT: In the meeting abstract?
MR. WONG: Yes.
BY MR. WONG:
Q. The abstract June, 2002. This data was published -- was this data published before the final study report for PALO-99-04 was written?
A. I believe it was.
Q. So this was preliminary with respect to the final study report?
A. Yes.
Q. Okay. And, based on this data, what were Helsinn scientists able to report in the conclusion?
MR. WONG: If you can blow up the conclusion.
THE WITNESS: They were able to conclude that palonosetron was effective at reducing the risk of emesis.

BY MR. WONG:

Q. And this was before the final study report was written?

A. Correct.

THE COURT: So this would be a chart of preliminary data?

THE WITNESS: Well, as I said before --

THE COURT: No, no.

THE WITNESS: The data are final. When the data is locked, that's it. And so this data was an analysis that was done on the locked data for 99-04 and presented at a meeting, but they hadn't written their final report yet. So there were other things, statistics and other things that might be done to analyze it.

MR. WONG: Thank you. No further questions.

RECROSS EXAMINATION BY MR. O'MALLEY:

Q. Pull up DTX-0264 again. Now, let's go to the table, I think the third page or so. Was it 009? There we go.

Now, you were talking about the ondansetron data. Do you recall that?

A. Yes.

Q. Now, this is data that was generated through 99-03, correct?

A. Yes.

Q. This isn't a historical efficacy data for ondansetron, correct?

A. Correct.
Q. Now, you said that the data showed non-inferiority of palonosetron, correct?
A. Yes.
Q. Now, then you showed -- then you stated that it maybe even shows that palonosetron's a little better. Do you recall that?
A. Yes.
Q. Now, you're aware that a non-inferiority study cannot be used to show superiority, correct?
A. Correct.
Q. Now, let's talk about Tang. Tang, and correct me if I heard you wrong, but I believe I heard that you don't believe that cancer patients in CINV -- experiencing CINV would also be on pain medications?
A. You know, most of my patients who are getting chemotherapy are not taking high doses of I.V. pain medications at the time they're getting their chemotherapy.
Q. At the moment they're getting their chemotherapy?
A. Correct.
Q. But they're getting pain medications, these cancer patients, at other times, correct?
A. Some of them.
Q. Yeah.
THE COURT: Including emetic-type pain meds?

BY MR. O'MALLEY:

Q. Opioids?

A. Yeah. So what happens is, when you're on a chronic opioid, you have what's called tachyphylaxis which is you get used to the side effects. So the nausea event from a morphine goes down over time, and so the people that are chronically treated for pain do not have the nausea from the pain medicine. It's the acute phase of giving it. So if postoperatively, they're given the morphine, they have that acute reaction.

Q. Now, going back to the MASCC abstract, I think it was PTX-0297. Now, counsel for Teva made the point that this is preliminary data. Did you hear that?

A. He did say that.

Q. Now, as I believe you've discussed today, you don't expect the data to change from the preliminary data to the final data; in fact, I think you've stated so strongly as it can't, correct?

A. Well, you have your data, and it is the data. Then you have your analysis of the data. And you could do different types of analysis.

Q. So --

A. So the preplanned analysis is the critical analysis that's in the protocol that is required for the FDA.

Q. So with respect --

A. And you can do it -- the first time you do it, I wouldn't call it preliminary. I would call it the first analysis of the locked database.

Q. So with respect to the preliminary data in here, it might have changed from here to the final study report?

A. I think the point was that --

Q. Yes or no? Could it have changed?

A. No.

Q. No. Thank you.

THE COURT: You mentioned that there's something about statistics, that they can do some more statistical analysis --

THE WITNESS: Yes.

THE COURT: -- after they get the preliminary data?

THE WITNESS: Yes.

THE COURT: But it doesn't change the raw numbers?

THE WITNESS: No.

THE COURT: Anything else?

MR. WONG: No further questions.

THE COURT: Thank you.

THE WITNESS: Thank you very much.

THE COURT: Thank you for traveling, Doctor, and safe travels home.

THE WITNESS: Thank you, ma'am.

(The witness left the stand.)

MR. LOMBARDI: And Your Honor -- yes.

THE COURT: I'll see counsel at the side off the record.

(A sidebar discussion was held off the record.)

(Proceedings adjourned at 3:58 p.m.)

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